

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Herausgegeben von der Kommission Mamma
(vertreten durch: Anton Scharl)
der Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
in der Deutschen Gesellschaft für Gynäkologie
und Geburtshilfe e.V.
sowie in der Deutschen Krebsgesellschaft e.V.

- ▶ Table of Contents
- ▶ Levels of Evidence and Grades of Recommendation
- ▶ Abbreviations
- ▶ Members of the AGO Breast Commission
- ▶ Conflict of Interest
- ▶ How to Use these Slides
- ▶ Editor & Copyright

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Table of Contents

Levels of Evidence and Grades of Recommendation

Abbreviations

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Guidelines of the AGO Breast Committee

- 1) Options for Primary Prevention: Modifiable Lifestyle Factors (Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren)
- 2) Breast Cancer Risk and Prevention (Brustkrebsrisiko und Prävention)
- 3) Early Detection and Diagnosis (Früherkennung und Diagnostik)
- 4) Pathology (Pathologie)
- 5) Prognostic and Predictive Factors (Prognostische und prädiktive Faktoren)
- 6) Lesions of Uncertain Malignant Potential (B3) – ADH, LIN, FEA, Papilloma, Radial Scar
(Läsionen mit unsicherem biologischem Potenzial (B3) – ADH, LIN, FEA, Papillom, Radiäre Narbe)
- 7) Ductal Carcinoma in situ (DCIS) (Duktales Carcinoma in situ (DCIS))
- 8) Breast Cancer Surgery Oncological Aspects (Operative Therapie des Mammakarzinoms unter onkologischen Aspekten)
- 9) Oncoplastic and Reconstructive Surgery (Onkoplastische und rekonstruktive Mammachirurgie)
- 10) Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
(Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen)
- 11) Adjuvant Cytotoxic and Targeted Therapy (Adjuvante zytostatische und zielgerichtete Therapien)
- 12) Neoadjuvant (Primary) Systemic Therapy (Neoadjuvante (Primäre) systemische Therapie)
- 13) Adjuvant Radiotherapy (Adjuvante Strahlentherapie)
- 14) Therapy Side Effects (Nebenwirkungen der Therapie)
- 15) Supportive Care (Supportive Therapie)
- 16) Breast Cancer: Specific Situations (Brustkrebs: Spezielle Situationen)
- 17) Breast Cancer Follow-Up (Brustkrebs Nachsorge)
- 18) Loco-regional Recurrence (Loko-regionäres Rezidiv)
- 19) Endocrine and "Targeted" Therapy in Metastatic Breast Cancer
(Endokrine und zielgerichtete Therapie des metastasierten Mammakarzinoms)
- 20) Chemotherapy with or without Targeted Drugs in Metastatic Breast Cancer
(Chemotherapie mit oder ohne zielgerichtete Substanzen beim metastasierten Mammakarzinom)
- 21) Osteooncology and Bone Health (Osteoonkologie und Knochengesundheit)
- 22) Specific Sites of Metastases (Besondere Situationen und Lokalisationen in der metastasierten Situation)
- 23) CNS Metastases in Breast Cancer (ZNS-Metastasen beim Mammakarzinom)
- 24) Complementary Therapy & Survivorship (Komplementäre Therapie & „Survivorship“)

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Oxford Levels of Evidence (LOE)

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| LOE | Therapy/Prevention, Aetiology/Harm | Prognosis |
|-----------|--|--|
| 1a | Systematic review (with homogeneity) of randomised controlled trials | Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations |
| 1b | Individual randomised controlled trials (with narrow Confidence Interval) | Individual inception cohort study with $\geq 80\%$ follow-up; clinical decision rule validated in a single population |
| 1c | All or none | All or none case-series |
| 2a | Systematic review (with homogeneity) of cohort studies | Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomised controlled trials |
| 2b | Individual cohort study (including low quality randomised controlled trials; e.g., $<80\%$ follow-up) | Retrospective cohort study or follow-up of untreated control patients in a randomised controlled trials; Derivation of clinical decision rule or validated on split-sample only |
| 2c | "Outcomes" Research; Ecological studies | "Outcomes" Research |
| 3a | Systematic review (with homogeneity) of case-control studies | |
| 3b | Individual Case-Control Study | |
| 4 | Case-series (and poor quality cohort and case-control studies) | Case-series (and poor quality prognostic cohort studies) |
| 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" | Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" |

Oxford Grades of Recommendation (GR)

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START

| | |
|----------|---|
| A | consistent level 1 studies |
| B | consistent level 2 or 3 studies <i>or</i> extrapolations from level 1 studies |
| C | level 4 studies <i>or</i> extrapolations from level 2 or 3 studies |
| D | level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level |

AGO Grades of Recommendation

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- ++** This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
- +** This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
- +/-** This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.
- This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
- This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

Abbreviations – I

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10+ LN

A
ABCSG-8
AC
ACR
AD
ADH
adj. A
AGO
AH
AI, AIs
ALH
A_{lip}
ALND
AML
ANC
AP
ARNO
ASCO
ATAC
autolog LADO
AxDiss
BC, bc
Bc-spec

BCS
BCSF
BCT
BIG 1-98
bilat.
Bip TRAM
BMD
BMI
BR
BRCA
BS-BM

≥ 10 tumor infiltrated axillary lymph nodes

Doxorubicin
Austrian Breast- and Colorectal Cancer Study Group
Doxorubicin / cyclophosphamide
American College of Radiology
Doxorubicin / docetaxel
Atypical ductal hyperplasia
Adjuvant doxorubicin
Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
Atypical hyperplasia
Aromatase inhibitor(s)
Atypical lobular hyperplasia
Liposomal doxorubicin
Axillary lymph node dissection
Acute myeloid leukemia
Absolute neutrophil count
Doxorubicin / paclitaxel
Arimidex® versus Nolvadex® (trial on adjuvant therapy)
American Society of Clinical Oncology
Arimidex®, Tamoxifen Alone or in Combination Trial
Autologous latissimus dorsi muscle flap
Axillary dissection
Breast cancer
Breast cancer specific

Breast conserving surgery
Breast cancer-free survival
Breast conserving therapy
Breast International Group
Bilateral
Bi-pedicled TRAM
Bone mineral density
Body mass index
Breast reconstruction
Breast cancer
Basic score for brain metastases (*Viani GA et al. BMC Cancer. 2007;7:53*)

Abbreviations – II

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| | |
|-------------|---|
| C | Cyclophosphamide |
| CA | Cancer |
| CAF | Cyclophosphamide / doxorubicin / 5-fluorouracil |
| Castr. | Castration |
| CB | Clinical benefit |
| CBC | Contralateral breast cancer |
| CBE | Clinical breast examination |
| Cc | CCNU (chemotherapy) |
| CC | Capsular contracture |
| CEA | Carcinoembryonic antigen |
| CEF | Cyclophosphamide / epirubicin / 5-fluorouracil |
| CEF 120 F | “Canadian FEC” (“Levine”): Cyclophosphamide/ <i>epirubicin 120</i> / 5-fluorouracil |
| CF | Cyclophosphamide / 5-fluorouracil |
| CGF | Cyclophosphamide / gemcitabine / 5-fluorouracil |
| CHF | Congestive heart failure |
| CHT | Chemotherapy |
| Circ. | Circulating |
| Cis / Capec | Cisplatin / capecitabine |
| CisG | Cisplatin / gemcitabine |
| CISH | Chromogenic in situ hybridization |
| CI | Confidence interval |
| CMF | Cyclophosphamide / methotrexate / 5-fluorouracil |
| CMFP | CMF + prednisolon |
| CNS | Central nervous system |
| CREC | Cardiac Review Evaluation Committee |
| CT | Computed (assisted) tomography |
| CTR | Control (group) |
| CTX | Chemotherapy |
| cum. Dose | Cumulative dose |
| CUP | Cancer of unknown primary |
| CYP2D6 | Cytochrome peroxidase P 450 2D6 |

Abbreviations – III

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D
D & C
D / Carbo
DAC
DARB
DC
DCIS
dd
DepoCyt®
DFI
DFS
DI
DIEP-flap
Doc + Cap
DOX, Doxo

E2, E₂
EBCTCG
EC
ECD
ECOG
ELISA
ENT
EORTC
Epi
EPO
ER
ErbB2

ESF
ETC
EWGBSP

Docetaxel
Dilatation and curettage
Docetaxel / carboplatin
Docetaxel / doxorubicin / cyclophosphamide
Darbepoetin
Docetaxel / cyclophosphamide
Ductal carcinoma in situ
Dose-dense
Liposomal cytarabine, liposomal ara-C
Disease-free interval
Disease-free survival
Dose intensity
Deep inferior epigastric perforator flap
Docetaxel + capecitabine
Doxorubicin

Estradiol
Early Breast Cancer Trialists' Collaborative Group
Epirubicin / cyclophosphamide
Extracellular-domain
Eastern Cooperative Oncology Group
Enzyme-linked immunosorbent assay
Ear-nose-throat (otorhinolaryngologic)
European Organization for Research and Treatment of Cancer
Epirubicin
Erythropoietin
Estrogen receptor
v-Erb-B2-erythroblastic leukemia viral oncogene homolog 2 = neuro-glioblastoma-derived oncogene homolog (avian) = human epidermal growth factor receptor = c-erbB2 = HER-2/neu = HER-2
Erythropoiesis-stimulating factor
Epirubicin / paclitaxel / cyclophosphamide (dose-dense chemotherapy)
European Working Group for Breast Screening Pathology

Abbreviations – IV

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F
F/U, f.-up
FA 60 C
FACT-F
FASG
FDG-PET / CT
FEA
FEC
FEC100
FISH
FNA / FNB / FNP
FSH
f-TRAM

G
GABG
GCP
G-CSF
GEICAM
GnRHa
GnRHa + AI
GOS
Gy

Hand-Foot-Sy.
Hb
HDCT
HER-2
high-dose / AST
HIP
HR
HRT

5-Fluorouracil
Follow-up
“US-FAC”: 5-Fluorouracil / *doxorubicin 60* / cyclophosphamide
Functional Assessment of Cancer Therapy (fatigue scale)
French Adjuvant Study Group
(18)F2-fluoro-D-2-desoxyglucose – Positron emission tomography / in combination with computed tomography
Flat epithelial atypia
5-Fluorouracil / epirubicin / cyclophosphamide
“French FEC”, (“Bonnetterre”): 5-fluorouracil / *epirubicin 100* / cyclophosphamide
Fluorescence in situ hybridization
Fine needle aspiration biopsy
Follicle stimulating hormone
Free TRAM-Flap

Gemcitabine
German Adjuvant Breast Cancer Group
Good clinical practice
Granulocyte-colony stimulating factors
Grupo Español de Investigación en Cáncer de Mamma (Spanish Breast Cancer Research Group)
Gonadotropin releasing hormone analogue / agonist
Gonadotropin releasing hormone analogue + aromatase inhibitor
Goserelin (Zoladex®)
Gray

Hand-foot-syndrome
Haemoglobine
High dose chemotherapy
Human epidermal growth factor receptor
High-dose chemotherapy with autologous stem cell transplantation
Health insurance plan
(Steroid) hormone receptor
Hormone replacement therapy

Abbreviations – V

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| | |
|-----------------------|---|
| I/S-GAP-GRACILIS-Flap | Inferior / superior gluteal artery perforator-flap and gracilis-flap |
| IBC | Inflammatory breast cancer |
| IBCSG | International Breast Cancer Study Group |
| ICE | Ibandronat Capecitabine Elderly |
| IES | International Exemestane Study |
| IGAP-Flap | Inferior gluteal artery perforator-flap |
| ICH | Immunohistochemistry |
| Inh. | Inhibitor |
| INT 0101 | Intergroup study 0101 |
| IR | Implant reconstruction |
| ITA | Italian Tamoxifen Anastrozole Trial |
| JCO | Journal of Clinical Oncology |
| Ki-67 | Kiel-antigen 67 (proliferation marker) |
| KPS | Karnofsky performance score |
| LABC | Locally advanced breast cancer |
| LADO, LDF | Latissimus dorsi muscle flap |
| LCIS | Lobular carcinoma in situ |
| LDH | Lactat dehydrogenase |
| LHRH | Luteinizing hormone releasing hormone |
| LIN | Lobular intraepithelial neoplasia |
| LITT | Laser-induced thermotherapy |
| LN | Lobular neoplasia |
| Lnn. | Axillary lymph nodes |
| LoE / GR | Level of evidence / grade of recommendation (Oxford Centre for Evidence-based medicine) |
| Locoreg | Loco-regional |
| LRR | Loco-regional recurrence |
| LVEF | Left ventricular ejection fractions |

Abbreviations – VI

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MBC
MDS
Med
Menop.
MG / MS
MIB
Mitox
Mo / mo
mod.
MPA/MA
MRI
MRM
MTX
MUGA
Mx

n.s., ns
N+
Nab-Paclitaxel
NAC
NBS
NCI-CTC2
NEAT / SCTBG
Neg.
NMR
NSABP
NSABP B14
NSABP B17
NSABP B20
NSABP B-33
NSABP P1-trial
NX
NYHA

Metastatic breast cancer
Myelodysplastic syndrome
Median
Menopause
Mammography / breast sonography
Minimal invasive breast biopsy
Mitoxantrone
Months
Modified
Medroxyprogesterone acetate / megestrol acetate
Magnetic resonance imaging
Modified radical mastectomy
Methotrexate
Multiple-gated acquisition scan
Mastectomy, mammography

Not significant
Node-positive
Nanoparticle-albumin-bound-paclitaxel
Nipple-areola-complex
National Breast Screening Study (Canada)
National Cancer Institute – Common Toxicity Criteria
National Epirubicin Adjuvant Trial / Scottish Cancer Trials Breast Group
Negative
MRI
National Surgery Adjuvant Breast and Bowel Project
NSABP Breast trial 14
NSABP Breast trial 17
NSABP Breast trial 20
NSABP Breast trial 33
NSABP Prevention trial 1
Vinorelbine / capecitabine
New York Heart Association

Abbreviations – VII

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| | |
|------------------------|--|
| OAS | Ovarian ablation or suppression |
| OFS | Ovarian function suppression |
| ONJ | Osteonecrosis of the jaw |
| OP | Operation |
| OR | Odds-ratio |
| ORR | Overall response rate |
| OS | Overall survival |
| OSNA | One-step nucleic acid amplification |
| Oxford | Oxford Centre for Evidence-based medicine levels of evidence and grades of recommendations |
| P + L | Paclitaxel + lapatinib |
| P weekly, Pw | Paclitaxel weekly |
| p.o., PO | Per os |
| Pac + Cap | Paclitaxel + capecitabine |
| PAI-1 | Plasminogen-activator inhibitor type I |
| PAP | PAP-Smear (Papanicolaou), cytologic test of the uterine cervix |
| PBI | Partial breast irradiation |
| PEG-Liposomal Doxo | Pegylated liposomal doxorubicin |
| PET | Positron emission tomography |
| PFS | Progression free survival |
| PgR | Progesterone receptor |
| PMMA | Polymethylmethacrylate |
| PMRT | Postmastectomy radiotherapy |
| Pos. Cells | Positive cells |
| prosp.-rand. Phase III | Prospective and randomized phase III |
| PS | Performance score |
| PST | Primary systemic therapy |
| Pts. | Patients |

Abbreviations – VIII

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| | |
|------------------------------------|--|
| R0 | No microscopic tumor residual |
| RAD | Radiotherapy |
| rand. Pat. | Patients randomized |
| RCT | Radiochemotherapy |
| Rec pos | Receptor positive |
| reg. CT + OP | Regional chemotherapy and operation |
| Rel. Risk | Relative risk |
| Reop | Re-operation |
| resp. | Respectively |
| RFA | Radiofrequency ablation |
| RFS | Recurrence-free survival |
| RPA | Recursive partitioning analysis |
| RR | Relative risk |
| RT | Radiotherapy |
| RT-PCR | Reverse transcriptase – polymerase chain reaction |
| S3 | Highest level of evidence based guidelines according to the Delphi-technique |
| SABCS | San Antonio Breast Cancer Symposium |
| Scottish CTPG and ICRF Breast Unit | Scottish Cancer Trials Breast Group and Imperial Cancer Research Foundation |
| SD | Standard deviation |
| SERD | Selective estrogen receptor down-regulator |
| SERM | Selective estrogen receptor modulator |
| SF | Shortening fraction |
| SGAP-flap | Superior gluteal artery perforator-flap |
| signals/nucl. | Signals per nucleus |
| SIRT | Selective internal radiation therapy |
| SN | Sentinel lymph node |
| SNB- | Sentinel lymph node negative (not tumor infiltrated) |
| SNE, SLNE | Sentinel lymph node excision |
| Solitary Meta. | Solitary metastasis |
| Sonogr. | Sonography |
| SPF | S-phase fraction |
| SSM | Skin-sparing mastectomy |
| supra-/infraclav | Supraclavicular, infraclavicular |
| SWE | Sweden |

Abbreviations – IX

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| | |
|----------|---|
| T | Taxane |
| TAM | Tamoxifen |
| TAM + C | Tamoxifen and chemotherapy |
| TBP | Treatment beyond progression |
| TCH | Docetaxel / carboplatin and trastuzumab |
| TEAM | Tamoxifen exemestane multicenter trial |
| Ther. | Therapy |
| TIA | Treatment-induced amenorrhea |
| TLI | Thymidine labelling index |
| Tox. | Toxicity |
| TRAM | Transverse rectus abdominis muscle |
| TT DR | Time to distant recurrence |
| TTR | Time to recurrence |
| UK/ANZ | United Kingdom / Australia and New Zealand |
| uPA | Urokinase-type plasminogen activator |
| Upper GI | Upper gastro-intestinal |
| US | Ultrasound |
| VAB | Vacuum-assisted breast biopsy |
| VAT | Video-assisted thoracoscopy |
| VATS | Video-assisted thoracical surgery |
| Vc | Vincristine |
| VNPI | Van Nuys Prognostic Index |
| Vomit. | Vomiting |
| WBI | Whole breast irradiation |
| WHO | World Health Organization |
| Wks | Weeks |
| XRT | Radiotherapy |
| Yrs. | Years |
| ZEBRA | Zoladex® Early Breast Cancer Research Association |

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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- **The members of the editing committee of these guidelines are specialists in diagnosis, treatment, and research in breast cancer. Most of the members therefore have cooperations with industry. Thus, potential conflict of interest cannot be excluded.**
- **In order to minimize potential bias within the statements we followed the pre-defined rules:**
 - **These guidelines are strictly based on available evidence from the scientific literature.**
 - **The chapters of each edition were prepared by annually alternating teams of authors.**
 - **Each statement and the correspondent AGO-recommendations were thoroughly discussed within the entire group and accepted by majority decisions.**
 - **Each member of the editing committee is required to submit a written declaration of his/her conflicts of interests to an elected internal COI committee on an annual basis.**
 - **Members who do not submit a COI declaration may not participate in the guideline preparation.**

Potential Conflicts of Interest (COI) 2013-2014

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All members of the AGO Breast Committee have submitted their COI report for the past year. Members of the AGO Breast Committee indicated that they have received support (e.g. research funding, lecture or consulting honoraria etc.) from the following entities:

Abraxis, American Diagnostica, Amgen, AstraZeneca, BMBF, BMS Medical, Boehringer Ingelheim, Celgene, Chugai, DFG, DKH, Eisai, Fresenius Biotech, Genentech, Genomic Health, GlaxoSmithKline, Hexal, Johnson&Johnson, Luisenkrankenhaus, medac, Medigene, Mentor, Merck, MSD, Mundipharma, Myriad Genetics, Nanostring, NeoDynamics, Novartis, Onkozept, Pfizer, Pharmamar, Philips Medical Systems, Prime Oncology, Roche, Sanofi-Aventis, Sividon Diagnostics, Teva, Willex, Zeiss.

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Diagnostik und Therapie von Patientinnen mit primärem und metastasierten Brustkrebs

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START

Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

Prävention

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- **Version 2012:**
Dall / Diel
- **Version 2013:**
Maass / Mundhenke
- **Version 2014:**
Scharl / Stickeler

Risikofaktoren für Brustkrebs

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Nicht modifizierbare Risikofaktoren

- **Höheres Alter**
- **Genetisches Risiko**
- **Familiäre Krebsanamnese**
- **Persönliche Brustanamnese**
 - Nicht-proliferative Läsionen
 - Proliferative Läsionen +/- Atypien
 - Hochrisikoläsionen (ADH, LIN)
 - Brustkrebs (DCIS, InvBC)
- **Brustdichte**
- **Thoraxbestrahlung**
- **Anzahl der Menstruationszyklen im Laufe des Lebens**

frühe Menarche, späte Menopause, mütterl. SS-Faktoren (z.B. Präeklampsie (Risikored.), Gestationsdiabetes und geringe phys. Aktivität während der SS (Risikoerhöhung))

Sozial definierte Risikofaktoren

Geringe Geburtenzahl oder keine Schwangerschaft
Höheres Alter bei erster Geburt

Risikofaktoren für Brustkrebs

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Modifizierbare Risikofaktoren

- **Wenig Stillen**
- **BMI < 18,5 und > 25 und besonders > 40 (Adipositas)**
- **Typ II Diabetes mellitus**
- **Nahrungszusammensetzung, Vitamin-D-Mangel**

Hormontherapie

- **Kürzlicher oraler Kontrazeptivagebrauch**
- **Hormontherapie (Östrogen/Gestagen- Kombination) in der Postmenopause**
- **Alkoholabusus**
- **Nikotin**
- **Schlafmangel (Nacht / Schichtarbeit)**
- **Verminderte körperliche Aktivität**
- **Chem. Noxen während der fetalen und frühkindl. Entwicklung**
 - **(DES, polyfluoroalkyl)**



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Home

The Expert Report »

Historical Overview

Business Plan

The People Behind the Report

Recommendations

The Policy Report »

**Communicating
the Reports »**

Resource Centre »

The Scientific Process »

**Continuous Update
Project »**

Our Global Network »

Contact Us

Useful Links

[Home](#) » [About the Report](#) » [Recommendations](#)

Recommendations

The Second Expert Report, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, features eight general and two special recommendations. The 10 recommendations are listed below. Together they comprise a blueprint that people can follow to help reduce their risk of developing cancer.

Click on each recommendation to find out more about it.

CHAPTER 12 of the Report features the recommendations in detail as does the Report **summary**.

BODY FATNESS

Be as lean as possible within the normal range of body weight

PHYSICAL ACTIVITY

Be physically active as part of everyday life

FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN

Limit consumption of energy-dense foods

Avoid sugary drinks

PLANT FOODS

Eat mostly foods of plant origin

ANIMAL FOODS

Limit intake of red meat and avoid processed meat

ALCOHOLIC DRINKS

Limit alcoholic drinks

PRESERVATION, PROCESSING, PREPARATION

Limit consumption of salt

Avoid mouldy cereals (grains) or pulses (legumes)

DIETARY SUPPLEMENTS

Aim to meet nutritional needs through diet alone

BREASTFEEDING (Special Recommendation)

Mothers to breastfeed; children to be breastfed

CANCER SURVIVORS (Special Recommendation)

Follow the recommendations for cancer prevention

The policy implications of the recommendations are explored in the **Policy Report**.

Präventiver Einfluss durch das Reproduktionsverhalten

Oxford / AGO
LoE / GR

- **Geburt(en)** 2b B
- **Anzahl der Schwangerschaften** 2b B
- **Erste ausgetragene Schwangerschaft \leq 30 Jahre** 2b B
- **Stillen** 3a B
(schützt, wenn Gesamtstilldauer
> 1,5–2 Jahre)

Geburten und Mammakarzinomrisiko

Ma et al. Breast Cancer Research 2006, 8:R43

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Prävention durch Änderung von Lifestyle-faktoren: Gewicht / Glucosestoffwechsel

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➤ **Einhaltung Normalgewicht (BMI 18,5 – 25 kg/m²)**

- **Prämenopausal**
- **Postmenopausal**

**Oxford / AGO
LoE / GR**

2a B ++

3a B ++

2a B ++

➤ **Vermeidung bzw. Früherkennung und Einstellung eines Typ II Diabetes mellitus**

2b B ++

(Reduktion der Brustkrebsinzidenz und -mortalität)

Prävention durch Änderung von Lifestylefaktoren: Ernährung

Oxford / AGO
LoE / GR

Nahrungsmuster

- **Mediterrane / gesunde > Westliche / ungesunde Nahrung**

2b B +

Nahrungszusammensetzung

- **Fettreduzierte Nahrung**
- **Vitamine, Mineralien, Spurenelem.**
- **Vitamin-D-Substitution zur Prävention**
- **Gemüse / Obst**
- **Phytoöstrogene / Soja**
- **Ballaststoffreiche Ernährung**

2a B +

2a B +/-

3a B +/-

2a B +/-

2a B +/-

1b A +

Prävention durch Änderung von Lifestylefaktoren: Alkohol

Oxford / AGO
LoE / GR

- **Reduktion des Alkoholkonsums
vermindert Brustkrebsrisiko** **2b B**

Insbesondere für

- **ER+/PgR+ Tumoren** **2b B**
- **Invasiv lobuläre Tumoren** **2b B**

Prävention durch Änderung von Lifestylefaktoren: Körperliche Aktivität

Oxford / AGO

LoE / GR

➤ Körperliche Aktivität

2a⁽⁻⁾ B ++

Metabolisches Equivalent zu 3–5 Std.

**Spaziergänge pro Woche mit
moderater Schrittgeschwindigkeit**

Prävention durch Lifestylefaktoren: Hormontherapie in der Postmenopause

Oxford / AGO
LoE / GR

➤ Vermeidung von Hormon- therapie in der Postmenopause

- | | | | |
|--|-----------|----------|------------|
| ➤ Vermeidung von Östrogen-/Gestagen-Kombinat. | 1b | A | + |
| ➤ Vermeidung von alleiniger Östrogentherapie (kein erhöhtes, evt. sogar verringertes Brustkrebsrisiko bei alleiniger Östrogentherapie, aber erhöhtes EM Ca Risiko) | 1b | A | +/- |

Prävention: Hormone (Östrogen + Gestagen-Kombination) in der Post-MP

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| | N | MC-RR(95%CI) | Weitere Aussagen |
|--|--|--------------------------------|--|
| WHI WHI: JAMA 2002 | ~ 27 000 | 1.3 (1,0-1,6) | 1,3 (1,1-1,6) Koronare Events 1,4 (1,1-1,9) Schlaganfälle 2,1 (1,4-3,3) Lungenembolien 2,1 (1,5-2,9) Thrombosen |
| HERS Hulley S: JAMA 2002 | I 2763 RCT, med. 4.1 J II 2321 open-label, 2.7J | 1.2 (0.95-1.5) | Med. Alter 67 J keine sekundäre Prävention Newkg. wie WHI + Cholezystektomien↗ |
| Million Women Beral V: Lancet 2003 | 1.084 110 ~ 50% HRT 4.1 J. follow-up | 1.66 (1.6-1.8) | EPC > E Art der Anwendung egal Einnahmedauer > 5 Jahre Tibolon RR 1.45 (1.2-1.7) |
| EPIC Int J Cancer 2010 | 1.153 747 person-years o | 1.4 (1.2-1.6) 1.8 (1.4-2.2) | E-Mono EPC > E |
| Metaanalyse Nelson HD: JAMA 2002 | 16 Studien | 1.21-1.40 | Newkg. wie WHI + |

Chlebowski SABCS 2010

Prävention durch Änderung von Lifestylefaktoren: Orale Kontrazeption (OC)

Oxford
LoE

- **Insgesamt erhöht die OC das Risiko für Mamakarzinom nicht**
- **Risiko für Mammakarzinom evtl. leicht erhöht, Risiko für Ovarial- und Endometriumkarzinom wird erniedrigt**

1a

1a⁽⁻⁾

OC und Mammakarzinomrisiko

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Cibula et al. Human Reproduction Update, Vol.16, No.6 pp. 631–650, 2010

Brustkrebsrisiko und Prävention

Brustkrebsrisiko und Prävention

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- **Versionen 2003–2013:**
**Schmutzler with Albert / Blohmer / Fehm /
Kiechle / Maass / Mundhenke / Thomssen**
- **Version 2014:**
Schmutzler / Rody

Allgemeine Prinzipien in der Prävention

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- Frauen mit einem erhöhten Erkrankungsrisiko für Brustkrebs sind Ratsuchende und nicht Patientinnen.
- Dem Angebot präventiver Maßnahmen geht eine umfassende und ausführliche Beratung mit Nutzen/Risikoabwägung voraus.
- Das Nichtschadensprinzip steht dabei im Vordergrund
(*Primum nil nocere*)

www.ago-online.de

Wer sollte auf Mutationen in den Genen BRCA1 und BRCA2 getestet werden?

Oxford LOE: 2b GR: B AGO: ++

Familien mit (je aus einer Familienseite) *

mindestens drei an Brustkrebs erkrankten Frauen unabh. vom Alter

mindestens zwei an Brustkrebs erkrankten Frauen, von denen eine vor dem 51 Lebensjahr (LJ) erkrankt ist

mindestens einer Brust- und einer an Eierstockkrebs erkrankten Frau

mindestens einer an Brust- und Eierstockkrebs erkrankten Frau

mindestens zwei an Eierstockkrebs erkrankten Frauen

mindestens einer an beidseitigem Brustkrebs erkrankten Frau mit einem Ersterkrankungsalter vor dem 51. LJ

mindestens eine an Brustkrebs erkrankte Frau vor dem 36. LJ

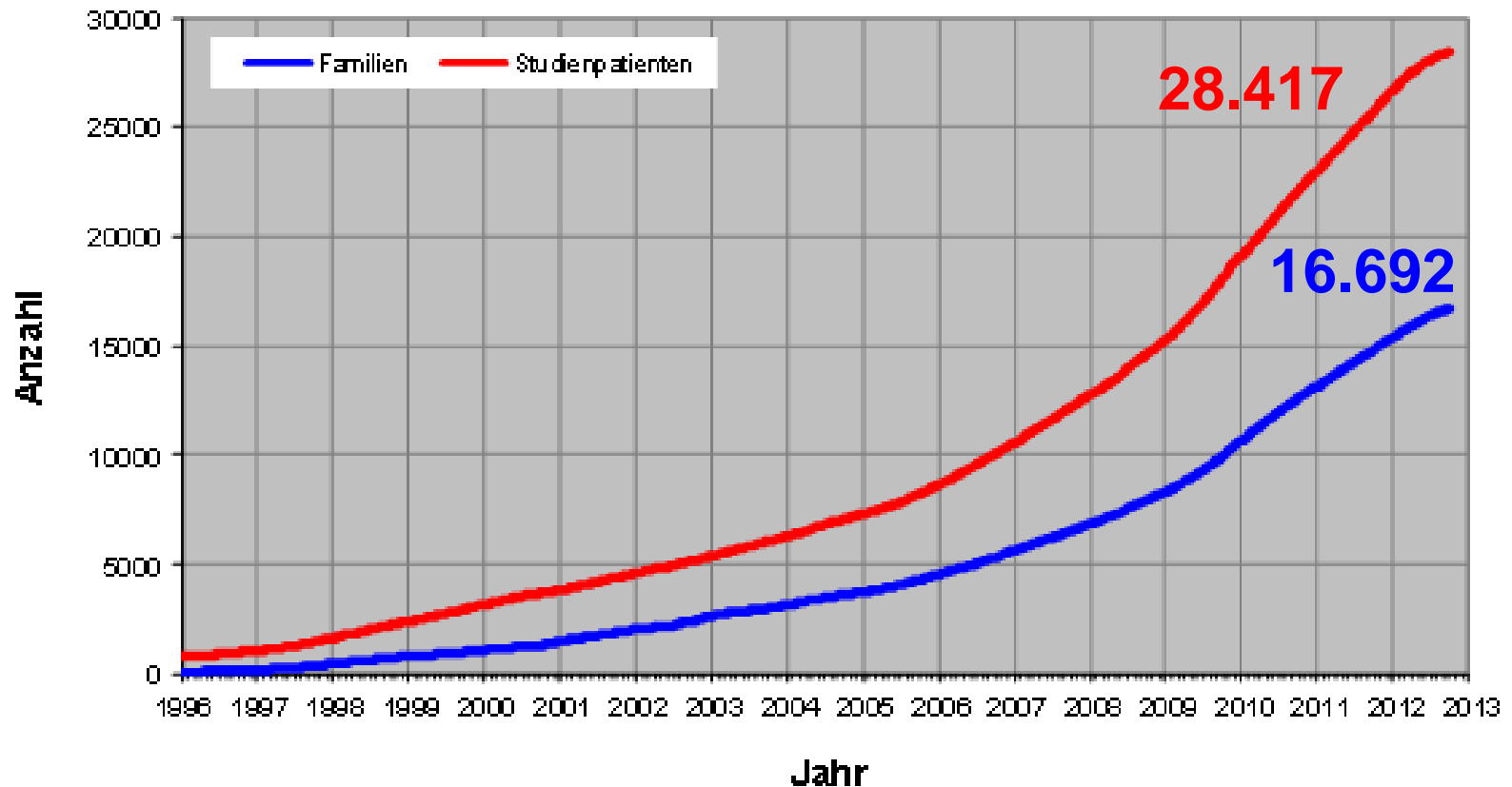
mindestens ein an Brustkrebs erkrankter Mann und mindestens ein/e weitere/r Erkrankte/r an Brust- oder Eierstockkrebs

***Einschlusskriterien (EK) des deutschen Konsortiums für Familiären Brust- und Eierstockkrebs (DK-FBEK) basierend auf der genetischen Analyse von >17.000 Familien; bei Vorliegen eines dieser EK liegt die Wahrscheinlichkeit für den Nachweis einer Mutation bei $\geq 10\%$**

Rekrutierung im Deutschen Konsortium Familiärer Brust- und Eierstockkrebs (DK-FBEK) bis 2013

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Checkliste zur Erfassung der Einschlusskriterien *

Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs

Name der Patientin:

Geburtsdatum:

A. Patientin und deren Geschwister / Kinder

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei der Patientin <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei der Patientin <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei der Patientin, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin <u>nach</u> dem 50. LJ | | 1 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin | | 2 | |
| eines Mamma-Karzinoms bei Schwestern/Töchtern <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei Schwestern/Töchtern, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei Schwestern/Töchtern <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei Brüdern/Söhnen | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei Schwestern/Töchtern | | 2 | |
| Summe Patientin / Geschwister / Kinder | | A | |

B. Mütterliche Linie

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei einem angehörigen Mann | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen | | 2 | |
| Summe mütterliche Linie | | B | |

C. Väterliche Linie

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei einem angehörigen Mann | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen | | 2 | |
| Summe väterliche Linie | | C | |

D. Der höhere Wert aus B und C

D

E. Summe aus A und D = Risiko-Score

A+D

Version: 03. Dezember 2012 (C) Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.

Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen.

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FORSCHEN
LEHREN
HEILEN

*Online über die Ärztekammer Westfalen-Lippe basierend auf den Kriterien des DK-FBEK:
www.aekwl.de/brustzentren-download

Varianten mit unklarer Bedeutung (VUS): 5-30% aller BRCA1/2-Mutationen

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Proposed Classification System for Sequence Variants Identified
by Genetic Testing

| Class | Description | Probability of being pathogenic |
|-------|--|---------------------------------|
| 5 | Definitely pathogenic | > 0.99 |
| 4 | Likely pathogenic | 0.95–0.99 |
| 3 | Uncertain | 0.05–0.949 |
| 2 | Likely not pathogenic or of little clinical significance | 0.001–0.049 |
| 1 | Not pathogenic or of no clinical significance | < 0.001 |

Testing Recommendations Associated With Each Class of Variant

| Class | Clinical testing | Surveillance recommendations if at-risk relative is positive | Research testing of family members |
|-------|---|--|--|
| 5 | Test at-risk relatives for variant | Full high-risk surveillance guidelines | Not indicated |
| 4 | Test at-risk relatives for variant ^a | Full high-risk surveillance guidelines | May be helpful to further classify variant |
| 3 | Do not use for predictive testing in at-risk relatives ^a | Based on family history (and other risk factors) | May be helpful to further classify variant |
| 2 | Do not use for predictive testing in at-risk relatives ^a | Treat as “no mutation detected” for this disorder | May be helpful to further classify variant |
| 1 | Do not use for predictive testing in at-risk relatives ^a | Treat as “no mutation detected” for this disorder | Not indicated |

^aRecommend continuing to test proband for any additional testing modalities available for the disorder in question; e.g., rearrangement testing.

VUS: Probleme und Fragen

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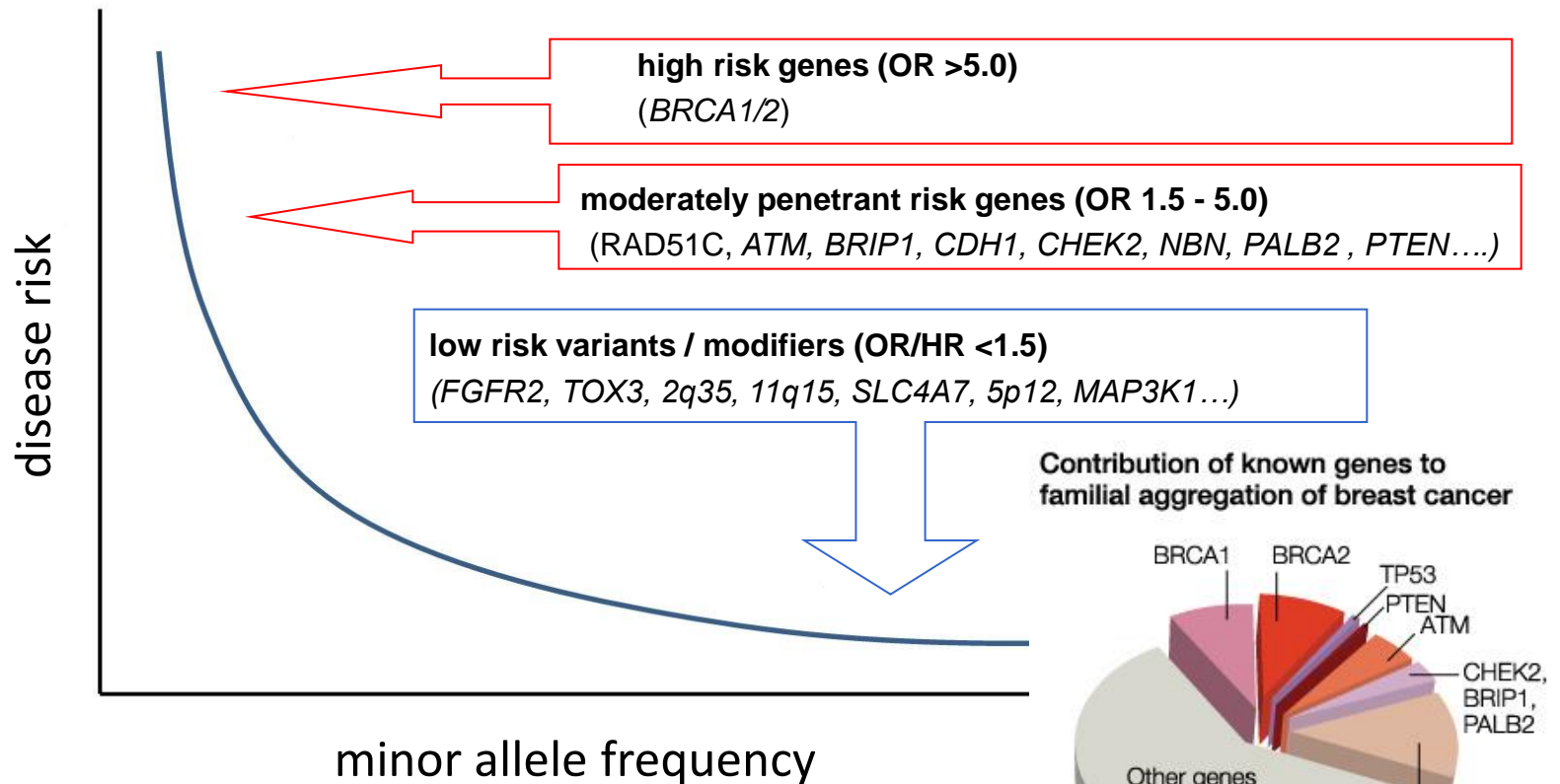
- Die meisten VUS sind private (>60%) oder sehr seltene Mutationen (≤ 3 , >80%)
- Zusätzliche Analysen zur Klassifizierung notwendig: e.g. Spleißanalysen, funktionelle, Segregations-, Co-occurrence Analysen, große Fall-/Kontrollstudien
- *in silico* Vorhersageprogramme (PolyPhen2, SIFT) sind für die klinische Interpretation nicht ausreichend
- VUS Klassifikation und klinische Entscheidungsfindung sind bisher nicht standardisiert

Stand der Forschung:

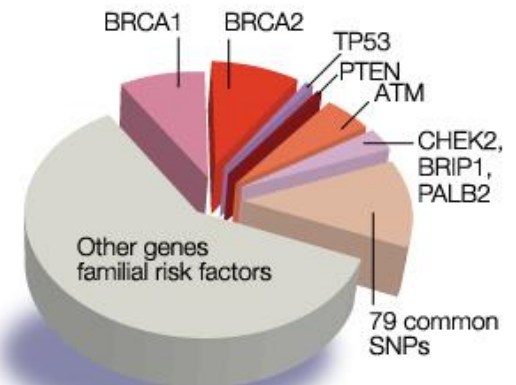
Oligogenetischer Erbgang und genetische Heterogenität

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Contribution of known genes to familial aggregation of breast cancer



Nicht BRCA-assoziierte erbliche Krebs syndrome mit erhöhtem Brustkrebsrisiko

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| Syndrome | Gene alteration | Lifetime Risk BC |
|--|--|---|
| Li Fraumeni | p53 | ~ 50 % ¹ |
| Cowden | PTEN | ~ 25 % ² |
| Hereditary diffuse gastric cancer syndrome | CDH1 | ~40-50 % (lobular) ³ |
| Peutz-Jeghers Syndrome | STK11/ LKB1 | ~45-50 % ⁴ Ovary: ~20 % Cervix: ~10 % Uterus: ~10 % |
| Lynch | mismatch repair MLH1, MSH2, MSH6, PMS2 | up to twofold increased risk compared to general population ⁵ Endometrial: ~ 25-60 % Ovary: up to 25 % |

www.ago-online.de

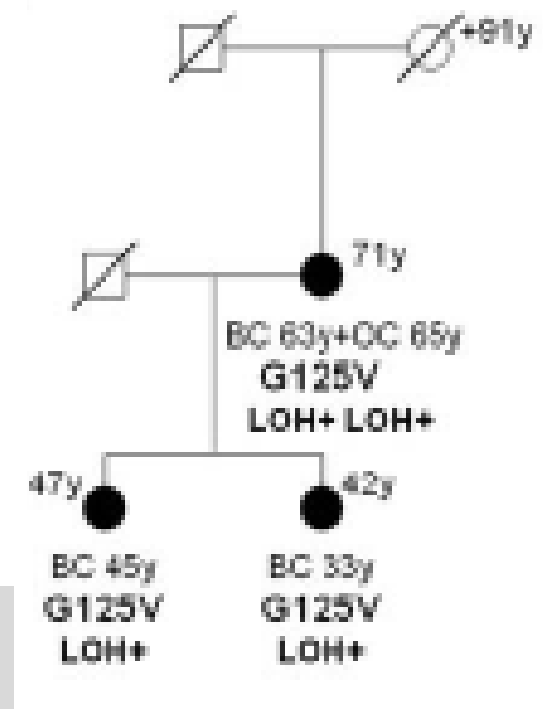
Empfehlung: genetische Beratung: GCP

Drittes Risikogen im DK-FBEK identifiziert

Germ-line mutations in breast and ovarian cancer pedigrees establish
RAD51C as a human cancer susceptibility gene

Nature Genetics April 18, 2010

Alfons Meindl¹, Heide Hellebrand^{1*}, Constanze Wiek^{2*}, Verena Erven², Barbara Wappenschmidt³, Dieter Niederacher⁴, Marcel Freund², Peter Lichtner⁵, Linda Hartmann⁶, Heiner Schaal⁶, Juliane Ramser¹, Ellen Honisch⁴, Christian Kubisch⁷, Hans E. Wichmann⁸, Karin Kast⁹, Helmut Deißler¹⁰, Christoph Engel¹¹, Bertram Müller-Myhsok¹², Kornelia Neveling¹³, Marion Kiechle¹, Christopher G. Mathew¹⁴, Detlev Schindler¹³, Rita K. Schmutzler³⁺, Helmut Hanenberg^{2,15+}



- 1.100 BRCA1/2 negative Risikofamilien:
670 Brustkrebs- (BC)- und 430 Brust- und Eierstockkrebs (BC/OC)-Familien
6 Mutationen in BC/OC Familien (**1.5%**)

Nicht validierte Brustkrebs Genpanels

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BROCA 40 gene panel (cross-cancer, <http://web.labmed.washington.edu/tests/genetics/BROCA>)

APC
ATM
ATR
BAP1
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK1
CHEK2
EPCAM
FAM175A
GALNT12
GEN1
GREM1
HOXB13
MLH1
MRE11A
MSH2
MSH6
MUTYH
NBN
PALB2
PMS2
PRSS1
PTEN
RAD50
RAD51
RAD51C
RAD51D
RET
SMAD4
STK11
TP53
TP53BP1
VHL
XRCC2

AMBRY Genetics BreastNext (16 genes) <http://www.ambrygen.com/tests/breastnext>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
MRE11A
MUTYH
NBN
PALB2
PTEN
RAD50
RAD51C
STK11
TP53

CEGAT CAN02: Brust- und Ovarialkarzom (30 genes) http://www.cegat.de/Tumorerkrankungen_171.html

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
EPCAM
FANCA
FANCC
FANCD2
FANCE
FANCF
FANGC
MEN1
MLH1
MRE11A
MSH2
MSH3
MSH6
NBN
PALB2
PMS1
PMS2
PTCH1
PTEN
RAD50
RAD51C
STK11
TP53

TruSight™ Cancer (Illumina) http://res.illumina.com/documents/products/5Cdatasheets/5Cdatasheet_trusight_cancer.pdf

AIP
ALK
APC
ATM
BAP1
BLM
BMPR1A
BRCA1
BRCA2
BRIP1
BUB1B
CDC73
CDH1
CDK4
CDKN1C
CDKN2A
CEBPA
CEP57
CHEK2
CYLD
DDB2
DICER1
DIS3L2
EGFR
EPCAM
ERCC2
ERCC3
ERCC4
ERCC5
EXT1
EXT2
EZH2
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANGC
FANCI
FANCL
FANCM
FH
FLCN
GATA2
GPC3
HNF1A

HRAS
KIT
MAX
MEN1
MET
MLH1
MSH2
MSH6
MUTYH
NBN
NF1
NF2
NSD1
PALB2
PHOX2B
PMS1
PMS2
PRF1
PRKAR1A
PTCH1
PTEN
RAD51C
RAD51D
RB1
RECQL4
RET
RHBDF2
RUNX1
SBDS
SDHAF2
SDHB
SDHC
SDHD
SLX4
SMAD4
SMARCB1
STK11
SUFU
TMEM127
TP53
TSC1
TSC2
VHL
WRN
WT1
XPA
XPC

CENTOGENE BC/OC panel (16 genes) <https://www.centogene.com/centogene>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
MRE11A
MSH6
NBN
PALB2
PTEN
RAD51
RAD51C
STK11
TP53

MYRIAD myRISK Panel (25 genes)

APC
ATM
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK2
EPCAM
MLH1
MSH2
MSH6
MUTYH
NBN
PALB2
PMS2
PTEN
RAD51C
RAD51D
SMAD4
STK11
TP53

Niedrigrisikovarianten aus genomweiten Assoziationsstudien (GWAS)

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| Locus | SNP | Häufigkeit | TOTAL BCAC | | FRR (%) |
|--------------|------------------|------------|-------------|---------------------------|-------------|
| | | | Odds Ratio | P-trend | |
| FGFR2 | rs2981582 | 38% | 1.24 | 5x10⁻⁸⁷ | 1.6% |
| TOX3 | rs3803662 | 25% | 1.21 | 8x10⁻⁵² | 1.1% |
| 2q35 | rs13387042 | 51% | 1.12 | 3x10 ⁻³⁴ | 0.5% |
| 11q15 | rs614367 | 15% | 1.20 | 5x10 ⁻¹⁶ | 0.5% |
| SLC4A7 | rs4973768 | 46% | 1.11 | 4x10 ⁻²³ | 0.4% |
| 5p12 | rs10941679 | 26% | 1.12 | 4x10 ⁻²³ | 0.4% |
| MAP3K1 | rs889312 | 28% | 1.11 | 3x10 ⁻²⁰ | 0.3% |
| 8q24 | rs13281615 | 40% | 1.10 | 8x10 ⁻¹⁵ | 0.3% |
| CASP8 | rs1045485 | 13% | 0.9 | 2x10 ⁻⁸ | 0.2% |
| ESR1 | rs2046210 | 33% | 1.09 | 2x10 ⁻¹⁵ | 0.2% |
| LSP1 | rs3817198 | 30% | 1.08 | 5x10 ⁻¹¹ | 0.2% |
| 1p11.2 | rs11249433 | 39% | 1.10 | 7x10 ⁻¹⁰ | 0.2% |
| ZNF365 | rs10995190 | 15% | 0.88 | 4x10 ⁻¹⁵ | 0.2% |
| ZMIZ1 | rs704010 | 39% | 0.92 | 3x10 ⁻⁸ | 0.1% |
| CDKN2A/B | rs1011970 | 17% | 1.08 | 7x10 ⁻⁸ | 0.09% |
| COX11 | rs6504950 | 27% | 0.95 | 10 ⁻⁸ | 0.07% |
| ANKRD16 | rs2380205 | 43% | 0.98 | 4x10 ⁻⁷ | 0.01% |
| RAD51L1 | rs999737 | 24% | 0.94 | 2x10 ⁻⁷ | 0.01% |

Low Risk Variants as Modifiers

Retrospective

Gaudet et al., in coop with GC-HBOC 2013: Combined genotype distribution of **14 variants** in 8,221 **BRCA2** mutation carriers (FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13)

- **Couch et al. in coop with the GC-HBOC 2013:** Combined genotype distribution of **10 variants** in 11,705 **BRCA1** mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1, TERT)
- 5% of BRCA1 carriers at lowest risk (28–50%) compared to the 5% at highest risk (81–100%)

Prospective

Mavaddat et al., 2013: combined genotype distribution of 7 low-risk SNP in **909 BRCA2 carriers**

BRCA2 carriers at the highest tertile of the score distribution were at significantly higher risk than women at the lowest tertile (HR = 4.1, 95%; CI = 1.2 to 14.5; P = .02)

first ‘proof of principle’

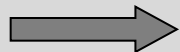
Associations are breast cancer subtype specific

Garcia-Closas et al., Clin Cancer Res, 2008

Genetically Defined Subtypes are Distinct Tumor Entities

Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:

- Typical histopathological features?
- Sensitivity to current screening modalities?
- Better survival of early detected tumors?
- Natural disease course?
- Response to anti-tumor therapy?



Genotype-phenotype-correlations must be employed

Current Clinical Impact of Other Risk Genes

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The remaining cancer susceptibility is most likely be transmitted by an oligo- or polygenic trait of moderate and low risk genes and alleles.

Moderate risk genes such as *RAD51C* exhibit very low mutation detection rates and may be associated with specific tumor subtypes.

Low risk variants confer only small risk elevations and also seem to be associated with specific tumor subtypes. Potential multiplicative effects that may be relevant for risk stratification and the provision of clinical prevention strategies remain to be elucidated.

Therefore genetic testing of moderate and low risk genes and variants should only be performed within large prospective cohort studies like the German Consortium for Hereditary Breast and Ovarian Cancer GC-HBOC.

Oxford / AGO LoE / GR

Clinical genetic testing for *RAD51C*; *CHEK2*

and/or other moderate risk genes, e.g. gene panels

2b **B** **-**

Clinical genetic testing for low risk variants

3b **D** **--**

Referral to centres of the GC-HBOC

5 **D** **++**

or cooperating centres

Voraussetzungen für die Einführung neuer prädiktiver oder diagnostischer genetischer Marker

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- Das Risikokollektiv ist durch klinisch-anamnestische Risikokriterien eindeutig identifizierbar
- Der positive prädiktive Wert der Risikokriterien im Hinblick auf das Vorliegen des genetische Risikofaktors ist bekannt
- Der Schwellenwert für eine genetische Testung ist in einem transparenten Konsensusprozess festgelegt worden
- Der genetische Test ist valide und reliabel
- Ein Spektrumbias wurde ausgeschlossen bzw. definiert
- Es existiert eine klinische Präventionsstrategie, die zur Mortalitätsreduktion durch Früherkennung oder Verhütung im Risikokollektiv führt

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Nicht-direktive Beratung vor der Durchführung präventive Maßnahmen

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- Berücksichtigung des Gendiagnostikgesetzes
- Berücksichtigung des Medizinproduktegesetzes, e.g. Risikokalkulation mittels Software-Programmen erfordert ein professionelles Training und Erfahrung
- Kommunikation absoluter Risiken in einem überschaubaren Zeitraum
- Kommunikation konkurrierender Risiken, e.g. Rezidiv- und Metastasierungsrisiko im Vergleich zum Zweitkarzinomrisiko bei bereits erkrankten Frauen
- Angemessene Bedenkzeit vor prophylaktischen Operationen

Definition von Frauen mit hohem Erkrankungsrisiko

Oxford / AGO LOE / GR

- **Mutation in den Genen BRCA1, BRCA2 oder RAD51C**
- **Heterozygotenrisiko $\geq 20\%$ oder verbleibendes Lebenszeitrisko $\geq 30\%$ (nach standardisiertem Prädiktionsmodell)**
- **Überlebende nach kindlichen Tumoren mit therapeutischer Radiatio der Brustwand (z.B. M. Hodgkin)**

1a A ++

2b B +

2a B ++

Multimodales Früherkennungsprogramm bei Frauen mit BRCA1/2 Mutation*

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➤ Zum Nachweis früher Tumorstadien

2a B ++

- | | | |
|------------------------------|------------|--------------|
| ➤ Ärztliche Tastuntersuchung | >=25 Jahre | halbjährlich |
| ➤ Ultraschall | >=25 Jahre | halbjährlich |
| ➤ Mammographie | >=40 Jahre | 1-2jährlich |
| ➤ Kernspintomographie | >=25 Jahre | jährlich |

➤ Zur Mortalitätsreduktion

5 D +

***Das Früherkennungsprogramm sollte an den Zentren für Familiären Brust- und Eierstockkrebs (GC-HBOC) oder kooperierenden Zentren durchgeführt werden. Die Adressen sind über die Deutsche Krebshilfe oder die S3-Leitlinie Mammakarzinom erhältlich).**

Modifizierte Früherkennungsprogramm bei Frauen aus BRCA-neg. Familien mit erhöhtem Risiko oder Überlebenden nach Morbus Hodgkin

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Rationale:

- Erhöhtes Brustkrebsrisiko bei Frauen nach Mantelfeldbestrahlung wegen Morbus Hodgkin im Kindes- und Jugendalter (8-18 Jahre)
- Erhöhtes Brustkrebsrisiko bei Frauen aus BRCA-negativen Risikofamilien, welches jedoch niedriger ist als für Frauen aus BRCA-positiven Familien
- Überweisung an die Zentren des DK-FBEK oder kooperierende Zentren zur Evaluation der Früherkennung und des Follow-up

Chirurgische Prävention bei gesunden BRCA1/2 Mutationsträgerinnen

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- **Prophylaktische bilaterale Salpingo-Oophorektomie (PBSO)**
 - Reduziert die Brustkrebsinzidenz und -mortalität
 - Reduziert die Eierstockkrebsinzidenz und -mortalität
 - Reduziert die Gesamtmortalität
- **Prophylaktische bilaterale Mastektomie (PBM)**
 - Reduziert die Brustkrebsinzidenz und -mortalität

2a B ++*

2a B +*

Die PBSO wird nach Abschluss der Familienplanung empfohlen

Die Ablate nach PBM zeigen eine erhöhte Rate an prämaligen Läsionen

*Studienteilnahme über die 15 Zentren für familiären Brust- und Eierstockkrebs empfohlen

Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer

Oxford / AGO
LoE / GR

- | | |
|--|--------------------------------|
| <ul style="list-style-type: none"> • Bilateral salpingo-oophorectomy (RR-BSO) reduces OvCa incidence and mortality reduces BrCa mortality reduces overall mortality (contradictory results for reduction of cl BrCa incidence) | 2b B ++* |
| <ul style="list-style-type: none"> • Bilateral mastectomy+ (RR-BM) reduces cl BrCa incidence | 2b B +/-* |
| <ul style="list-style-type: none"> • Tamoxifen (reduces cl BrCa incidence) | 2b B +/-* |
| <ul style="list-style-type: none"> • Indication for PBM should consider age at onset of first breast cancer and the affected gene | 2a B +++* |

+ Overall prognosis has to be considered

***Study participation recommended**

PBSO und Mortalitätsreduktion

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Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality^a

| | All Eligible Women | | | No Prior Breast Cancer ^b | | | Prior Breast Cancer ^c | | |
|---|---------------------|---------------------|---------------------|-------------------------------------|---------------------|---------------------|----------------------------------|---------------------|---------------------|
| | Total (n = 2482) | BRCA1 (n = 1587) | BRCA2 (n = 895) | Total (n = 1458) | BRCA1 (n = 935) | BRCA2 (n = 523) | Total (n = 1027) | BRCA1 (n = 654) | BRCA2 (n = 373) |
| Risk-reducing salpingo-oophorectomy | | | | | | | | | |
| Yes | 993 (40.0) | 706 (44.5) | 287 (32.1) | 447 (30.7) | 327 (35.0) | 120 (22.9) | 451 (43.9) | 317 (48.5) | 134 (35.9) |
| Deaths | 31 (3.1) | 25 (3.5) | 6 (2.1) | 8 (1.8) | 8 (2.4) | 0 | 19 (4.2) | 14 (4.4) | 5 (3.7) |
| No | 1489 (60.0) | 881 (55.5) | 608 (67.9) | 1011 (69.3) | 608 (65.0) | 403 (77.1) | 576 (56.1) | 337 (51.5) | 239 (64.1) |
| Deaths | 146 (9.8) | 93 (10.6) | 53 (8.7) | 60 (5.9) | 43 (7.1) | 17 (4.2) | 92 (16.0) | 54 (16.0) | 38 (15.9) |
| Age, mean (range), y | | | | | | | | | |
| At time of risk-reducing oophorectomy | 45.4 (20.5-79.0) | 44.5 (20.5-79.0) | 47.6 (30.4-72.9) | 43.2 (20.5-79.0) | 42.1 (20.5-79.0) | 46.4 (33.0-68.5) | 47.6 (29.7-75.2) | 47.0 (29.7-75.2) | 49.1 (30.4-72.9) |
| At start of follow-up for those without oophorectomy | 39.8 (18.1-90.4) | 38.5 (18.2-90.4) | 41.6 (18.1-82.7) | 36.3 (18.1-90.4) | 35.1 (18.2-90.4) | 38.2 (18.1-82.7) | 45.3 (21.9-86.2) | 44.2 (21.9-86.2) | 46.9 (26.1-77.7) |
| Follow-up, mean (range), y | | | | | | | | | |
| To death | 6.0 (0.5-23.5) | 5.9 (0.6-22.3) | 6.2 (0.5-23.5) | 9.0 (0.96-23.5) | 8.5 (1.0-22.3) | 10.3 (2.8-23.5) | 4.6 (0.5-20.3) | 4.3 (0.6-20.3) | 5.1 (0.5-13.3) |
| To censoring | 5.0 (0.5-27.9) | 5.0 (0.5-27.7) | 4.9 (0.5-27.9) | 5.8 (0.5-27.9) | 5.7 (0.5-27.7) | 5.9 (0.5-27.9) | 4.5 (0.5-24.6) | 4.8 (0.5-24.6) | 4.1 (0.5-15.4) |
| All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI) ^d | | | | | | | | | |
| Age <50 y | 0.40 (0.26-0.61) | 0.38 (0.24-0.62) | 0.52 (0.22-1.23) | 0.45 (0.21-0.95) | 0.52 (0.24-1.14) | No deaths | 0.30 (0.17-0.52) | 0.26 (0.13-0.52) | 0.45 (0.17-1.16) |
| Age ≥50 y | 0.41 (0.25-0.67) | 0.40 (0.24-0.68) | 0.16 (0.02-1.30) | 0.70 (0.31-1.57) | 0.50 (0.21-1.20) | No deaths | 0.28 (0.14-0.55) | 0.30 (0.14-0.64) | 0.19 (0.02-1.59) |
| Age ≥50 y | 0.37 (0.15-0.94) | 0.22 (0.06-0.85) | 0.47 (0.12-1.80) | 0.28 (0.03-2.42) | 0.93 (0.11-8.12) | No deaths | 0.37 (0.13-1.03) | 0.12 (0.02-0.73) | 0.46 (0.10-2.13) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aValues are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

^bThere were no breast cancer cases prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.

^cBreast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

^dAdjusted for year of birth and stratified by center.

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LEHREN
HEILEN

Domchek et al. JAMA 2010; Table 4.

Kontralaterales Brustkrebsrisiko in 6235 BRCA1/2 positiven und negativen Frauen (retrospektiv)

Rhiem *et al. Breast Cancer Research* 2012, **14**:R156
<http://breast-cancer-research.com/content/14/6/R156>

Page 6 of 8

Table 2 Cumulative risks (in %) and 95% confidence intervals (in parentheses) for contralateral breast cancer depending on age at first breast cancer observed in relatives of index patients.

| | <i>BRCA1</i> | <i>BRCA2</i> | <i>BRCA negative</i> |
|--|------------------|------------------|----------------------|
| Age at first breast cancer < 40 years | | | |
| 5 years after first breast cancer | 14.1 (10.1-18.0) | 2.9 (0.0-6.3) | 4.8 (2.6-6.9) |
| 10 years after first breast cancer | 30.1 (24.0-36.2) | 18.2 (7.9-28.5) | 10.6 (6.8-14.4) |
| 15 years after first breast cancer | 40.8 (33.2-48.3) | 20.9 (9.7-32.1) | 15.3 (10.4-20.3) |
| 25 years after first breast cancer | 55.1 (45.4-64.9) | 38.4 (18.5-58.2) | 28.4 (20.5-36.3) |
| Age at first breast cancer 40-49 years | | | |
| 5 years after first breast cancer | 9.2 (5.8-12.5) | 6.9 (2.7-11.1) | 4.2 (2.9-5.5) |
| 10 years after first breast cancer | 16.7 (11.7-21.7) | 13.4 (7.0-19.8) | 8.4 (6.3-10.5) |
| 15 years after first breast cancer | 23.2 (16.9-29.6) | 22.0 (12.1-31.9) | 10.7 (8.1-13.3) |
| 25 years after first breast cancer | 44.5 (33.2-55.7) | 40.5 (22.4-58.6) | 18.1 (13.9-22.3) |
| Age at first breast cancer ≥ 50 years | | | |
| 5 years after first breast cancer | 7.1 (3.8-10.5) | 3.5 (0.9-6.1) | 3.6 (2.7-4.5) |
| 10 years after first breast cancer | 11.4 (6.5-16.3) | 10.4 (4.9-16.0) | 5.5 (4.3-6.7) |
| 15 years after first breast cancer | 18.7 (11.0-26.3) | 15.5 (7.8-23.3) | 8.1 (6.3-9.9) |
| 25 years after first breast cancer | 21.6 (12.3-30.8) | 15.5 (7.8-23.3) | 12.9 (8.9-17.0) |
| Total | | | |
| 5 years after first breast cancer | 10.4 (8.3-12.5) | 4.5 (2.5-6.5) | 3.9 (3.2-4.6) |
| 10 years after first breast cancer | 20.4 (17.1-23.7) | 13.2 (9.2-17.2) | 7.1 (6.0-8.2) |
| 15 years after first breast cancer | 28.7 (24.4-32.9) | 19.0 (13.5-24.4) | 9.9 (8.5-11.4) |
| 25 years after first breast cancer | 44.1 (37.6-50.6) | 33.5 (22.4-44.7) | 17.2 (14.5-19.9) |

Therapie des BRCA1/2-assoziierten Mammakarzinoms⁺

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**Es liegen prospektive Kohortenstudien mit begrenzter
Nachbeobachtungszeit vor**

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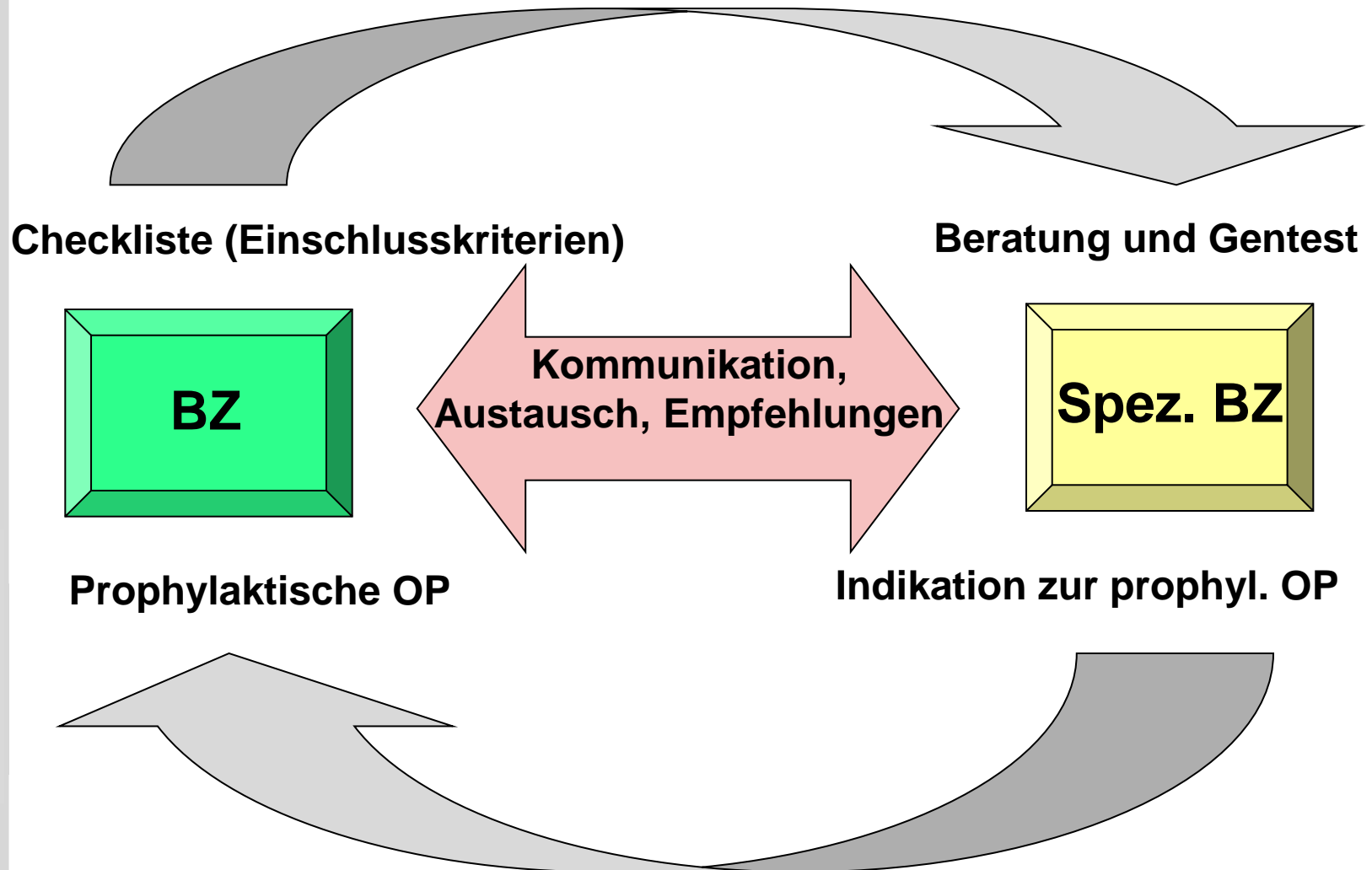
- **Brusterhaltende OP:
Adäquate lokale Tumorkontrolle (~10 Jahre Follow-up)** **2a B +**
- **Systemische Therapie nach den allgemeinen Standards** **3a B +**
- **BRCA1 Mutationsstatus ist ein prädiktiver Faktor für
das Ansprechen auf Chemotherapie** **3b B +**
- **Platinum-basierte Regime** **3 B +/-***
- **PARP-Inhibitoren bei metastasiertem Mammakarzinom** **2a B +/-***

+ Gesamtprognose muss berücksichtigt werden * Studienteilnahme empfohlen

Kooperation von Brustzentren (BZ) mit spezialisierten Zentren des DK-FBOK

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Medikamentöse Prävention für Frauen mit erhöhtem Risiko

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- **Tamoxifen für Frauen > 35 Jahre**
Reduktion des invasiven MaCa, DCIS und LN **1a A +***
- **Raloxifen für postmenopausale Frauen**
Reduktion des invasiven MaCa **1b A +***
- **Aromatasehemmer für postmenopausale Frauen** **1b A +[#]**

Signifikante Risikoreduktion unter Anastrozol für Ovarial- und Endometriumkarzinome, sowie Haut-, Kolorektal-, Schilddrüsen-, Harnwegskarzinome und hämatologische Tumoren

Chemopräventive Therapien sollten nur nach individueller und umfassender Beratung angeboten werden. Der Nutzen hängt vom Risikostatus, Alter und vorbestehenden Risiken für Nebenwirkungen ab.

***Risiko definiert wie in der NSABP P1-Studie (1.66% in 5 Jahren)**

Risikoreduktion für das ipsi- und kontralaterale Mammakarzinom

Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein kontralaterales Zweitkarzinom

➤ **Tamoxifen***

➤ **Aromatasehemmer***

➤ **GnRHa + Tamoxifen***

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LOE / GR**

1a A +

1a A +

1b B +

***Nur für das HR positive sporadische MaCa belegt**

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Früherkennung und Diagnostik

Früherkennung und Diagnostik

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- **Version 2005–2013:**
**Albert / Blohmer / Fersis /
Junkermann / Maass / Scharl /
Schreer**

- **Version 2014:**
Schreer / Blohmer

Früherkennung Mammographie

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| Alter | Intervall | Oxford | | AGO |
|--------|-----------|--------|----|-----|
| | | LOE / | GR | |
| < 40 | na | - | - | -- |
| 40–50 | 12–18 | 1b | B | + |
| 50–70* | 24 | 1a | A | ++ |
| > 70 | 24 | 4 | C | + |

Brustkrebs Mortalitätsreduktion

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Metaanalysen

RR 95%CI

Independent UK Panel, 2012

13-year metaanalysis

0.80 (0.73–0.89)

Cochrane Review, 2011

Fixed-effect metaanalysis of 9 RCT-trials

0.81 (0.74–0.87)

As above, but excluding women <50 years

0.77 (0.69–0.86)

US Task Force, 2009

Women 50–59 years

0.86 (0.75–0.99)

Women 60–69 years

0.68 (0.54–0.87)

Estimates weighted average

0.81

Canadian Task Force, 2011

Women aged 50–69 years

0.79 (0.68–0.90)

Duffy et al, 2012

Review of all trials and age groups

0.79 (0.73–0.86)

Mammographie-Screening

Frauen 40–49 Jahre

| | |
|--------------------------------|-------------------------------|
| RR (eingeladene Frauen) | 0.74 (95%CI 0.66-0.83) |
| 40–44 J | 0.83 (95%CI 0.67-1.00) |
| 45–49 J | 0.68 (95%CI 0.59-0.78) |
| Teilnehmerinnen | 0.71 (95%CI 0.62-0.80) |

NNS **1252 (95%CI 958-1915)**
(1 live saved / 10 years screening)

Früherkennung Sonographie

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- **Screening-Mammasonogr.**
 - **Autom. 3D-Sonographie**

| | | |
|-----------|----------|------------|
| 5 | D | - - |
| 3b | C | - - |

Als Ergänzung bei:

- **Dichtem Parenchym (ACR 3–4)**
 - **Erhöhtem Risiko**
- **Mammographischer Läsion**
- **Zur Abklärung susp. Läsionen im MRT**

| | | |
|-----------|-----------|-----------|
| 2b | B | ++ |
| 1b | C* | ++ |
| 3b | B | ++ |
| 2b | C | ++ |

Früherkennung

Klinische Untersuchung

**Oxford / AGO
LOE / GR**

Als alleinige Untersuchung

- | | | | |
|---|-----------|----------|-----------|
| ➤ Selbst-Untersuchung | 1a | A | -* |
| ➤ Klinische Untersuchung (CBE) durch ärztliches Personal | 3b | C | -* |
| ➤ CBE wegen mammo/sonographischer Läsion | 5 | D | ++ |

CBE in Kombination mit Bildgebung

BCP **++**

* Kann Brust-Bewußtsein erhöhen

Abklärung von Symptomen

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| | | | |
|-------------------------------------|-----------|----------|------------|
| ➤ Klinische Untersuchung | 3b | B | ++ |
| ➤ Mammographie | 1b | A | ++ |
| ➤ Tomosynthese | 3b | C | +/- |
| ➤ Sonographie | 2b | B | ++ |
| ➤ Elastographie (Shear wave) | 3b | C | + |
| ➤ Autom. 3D-Sonographie | 3b | C | +/- |
| ➤ MRT* | 2b | D | +/- |
| ➤ Minimalinvasive Biopsie | 1c | A | ++ |

*Wenn klinische, mammographische und sonographische Diagnostik keine endgültige Diagnose erlauben

Prätherapeutische Abklärung und Staging

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| | Oxford LOE / GR | / | AGO |
|------------------------------------|--------------------|----------|------------|
| ➤ Klinische Untersuchung | 5 | D | ++ |
| ➤ Mammographie | 2b | B | ++ |
| ➤ Sonographie | 2b | B | ++ |
| ➤ Axillasono.+ Biopsie/FNA | 2b | B | + |
| ➤ MRT* | 1b | B | +/- |
| ➤ Minimalinvasive Biopsie** | 1b | A | ++ |

* Die Möglichkeit der MRT-gestützten Biopsie ist Voraussetzung für die MRT-Untersuchung.
Einzelfall-Entscheidung z.B. Hochrisiko, dichtes Drüsengewebe und invasiv lobulärer Tumor, V. a.
multifokale /-zentrische Tumorausbreitung. Keine Reduktion der Nachresektionsrate.

** Wenn klinische Untersuchung, Mammographie und Sonographie (ggf. plus MRT)
keine exakte Ausdehnungsbeurteilung erlauben.

MRT: Präoperatives Staging?

| | |
|--|--------------------|
| Falsch-negativ Rate | 4–12 % |
| Falsch-positiv Rate | bis zu 40 % |
| Nicht seltener R1-Resektionen | |
| Odds-Ratio für die Mastektomie | 1,80 |
| Verzögerung des Therapiebeginns | 22,4 Tage |

MRT: Präoperatives Staging

- **9 ausgewählte Studien (2 randomisiert; 7 Kohortenstudien)**
- **3112 Patientinnen mit Mammakarzinom**
- **MRT versus kein-MRT:**
 - **Initiale Mastektomie 16,4% versus 8,1% [OR, 2,22 (P < 0,001); adjusted OR, 3,06 (P < 0,001)]**
 - **Nachresektion nach initialer BET 11,6% versus 11,4% [OR, 1,02 (P = 0,87); adjustiert OR, 0,95 (P = 0,71)]**
 - **Gesamt Mastektomierate 25,5% versus 18,2% [OR, 1,54 (P < 0,001); adjustierte OR, 1,51 (P < 0,001)]**

N Houssami et al. Ann Surg 2013; 257

MRT: Präoperatives Staging bei Lobular Invasive Breast Cancer

- **766 patients with invasive lobular cancer (ILC)**
 - **initial mastectomy: 31.1% versus 24.9% [OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]**
 - **re-excision after initial breast conservation 10.9% versus 18.0% [OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]**
 - **overall mastectomy 43.0% versus 40.2% [OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]**

COMICE Trial (RCT)

MRT präop. vs. kein präop. MRT

Ergebnisse

Randomisierung von 816 Patientinnen mit MRT und 807 ohne MRT. Die zusätzliche MRT-Diagnostik zur konventionellen Trippel-Diagnostik reduziert nicht die Nachresektion- oder die Mastektomierate.

(Nachoperationen in der MRT-Gruppe $n = 153$ (19%) versus 156 (19%) in der Gruppe ohne MRT, odds ratio 0.96, 95% CI 0.75—1.24; $p=0.77$)

Schlussfolgerung

- Keine signifikante Nachresektionsreduktion
- Mehr Kosten mit geringem bzw. keinem Benefit

MONET Trial (RCT)

Routine-Versorgung vs. präoperatives MRT

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| | Pos. Schnitttrand | Zusätzl. OPs |
|---------------------------|-------------------|-----------------|
| Routine-Versorgung | 12% | 28% |
| Präoperatives MRT | 34% | 45% |

„ Breast MRI should not be used routinely for preoperative work-up of patients with non-palpable breast cancer.“

MRT Screening (Hoch-Risiko-Gruppe) Nutzen

- **Frühe Erkennung von Mammkarzinomen zusätzlich zur konventionellen Bildgebung**
- **Prognoseverbesserung?
(Mortalitätsreduktion? Reduktion der Intervallkarzinome?)**

MRT-Screening (Hoch-Risiko-Gruppe) Probleme

| MRT zusätzlich zur Mammographie | RR |
|--|-----------|
| Abklärung benigner Läsionen | 3,43–4,86 |
| Biopsien mit benignem Befund | 1,22–9,50 |
| Operative Eingriffe benigner Befunde (MARIBS) | 2 |
| Falsch-negatives MRT (MRISC) | 22% |

Falsch-negatives MRT bei Hochrisiko-Frauen (MRISC)

- **97 maligne Mammatumoren**
19 /97 (20%) DCIS
- **21 /97 (22%) falsch-negativ**
9 /21 (20%) DCIS

**„.....Necessity of screening not only with
MRI but also with mammography.“**

Obdeijn IMA et al. 2010

MRT und DCIS

| Studie | Anzahl Untersuchungen | Zuverlässigkeit (%) | Sensitivität (%) | Spezifität (%) |
|----------------------|-----------------------|---------------------|------------------|----------------|
| Gilles et al 1996 | 172 | 70 | 95 | 51 |
| Westerhof et al 1998 | 63 | 56 | 45 | 72 |
| Bazzocchi et al 2006 | 112 | 80 | 79 | 68 |
| Kuhl et al 2007 | 75 | - | 88 | - |
| Baur et al. 2013 | 58 | | 79,3 | |

„Ein negativer MRT-Befund kann nicht als Beweis für Gutartigkeit gewertet werden.“

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Pathologie

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- **Versionen 2004–2013:**
Costa / Fehm / Huober / Kreipe / Lück / Sinn / Thomssen
- **Version 2014:**
Kreipe / Friedrichs

Aufarbeitung von Stanzbiopsien (Ultraschall gesteuert / stereotaktisch)

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|------------|
| ➤ Aufarbeitung in Schnittstufen (14G: min. 3 Stufen / 11G, 8G: 6-8 Stufen) | 5 | D | ++ |
| ➤ Radiologisch-pathologische Korrelation (Mikrokalk / Dichte), Anwendung der B-Klassifikation | 1b | B | ++ |
| ➤ Schnellschnittdiagnostik an Stanzbiopsien | 5 | D | - - |
| ➤ Evaluation des ER/PgR und HER2-Status | 3b | C | ++ |
| ➤ Umlaufzeit < 24 h (Dignität) | 5 | D | + |
| ➤ Optimale Fixationszeit 6 – 48 h | 5 | D | ++ |
| ➤ Standardisierung der Fixation und Prozessierung | 5 | D | ++ |
| ➤ Teilnahme an QM-Maßnahmen | 3 | D | ++ |

Feinnadel-Aspirations-Zytologie*

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- **Mamillensekret**
- **Tumor***
- **Zyste**
- **Lymphknoten**

| Oxford / LoE / GR | AGO |
|----------------------|-----|
|----------------------|-----|

| | | |
|---|---|---|
| 5 | D | + |
|---|---|---|

| | | |
|---|---|---|
| 5 | D | - |
|---|---|---|

| | | |
|---|---|-----|
| 5 | D | +/- |
|---|---|-----|

| | | |
|---|---|-----|
| 5 | D | +/- |
|---|---|-----|

*** Ultraschall geleitete Stanzbiopsie empfohlen**

Indikationen zur intraoperativen pathologischen Sofortuntersuchung einschließlich Schnellschnitt

Oxford / AGO
LoE /GR

- | | | | |
|---|----------|----------|------------|
| ➤ Sentinelbiopsie beim invasiven Karzinom | | | |
| - bei klinischer Konsequenz | 5 | D | + |
| - bei nicht zu erwartender Konsequenz (z.B. cT1 or cT2 und cN0 und BET) | 5 | D | +/- |
| ➤ Beurteilung der Resektionsränder | | | |
| - wenn makroskopisch < 1 cm | 5 | D | + |
| - wenn makroskopisch > 1 cm | 5 | D | - |
| ➤ Läsion mit einer Größe von ≥ 1 cm, keine Corebiopsie erfolgt | 5 | D | + |
| ➤ Nicht tastbare Läsion oder Läsion < 1 cm | 5 | D | -- |
| ➤ Asservierung von unfixiertem Nativgewebe | 5 | D | + |

Allgemeine Empfehlungen zur pathologischen Bearbeitung

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|-----------|
| ➤ Zuschnitt und Aufarbeitung entsprechend publizierten Protokollen und Leitlinien mit dem Ziel einer exakten Bestimmung von Tumorgröße und Randsituation | 5 | D | ++ |
| ➤ Berücksichtigung der Bildgebung (z.B. Mikroverkalkungen, Multifokalität) und der Topographie | 5 | D | ++ |
| ➤ Präparateradiographie bei nicht palpablen Läsionen und Mikroverkalkungen | 5 | D | + |
| ➤ Eine minimale Fixationszeit von 6 (bis max. 48 h) ist einzuhalten zur Vermeidung von Schrumpfungsartefakten und Beurteilung einer Angioinvasion | 5 | D | + |
| ➤ Asservierung von Frischgewebe für Gewebebanken durch oder in Kooperation mit Pathologie | 5 | D | + |

Aufarbeitung bei brusterhaltender Therapie

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|-----------|
| ➤ Die Lamellierung erfolgt senkrecht zur Längsachse (bzw. bei kugeligen Exzidaten senkrecht zur Mamillen-Peripherie-Achse) | 5 | D | ++ |
| ➤ Systematisches Sampling, mindestens ein Gewebeblock pro cm Resektat | 5 | D | ++ |
| ➤ Tuschemarkierung der Resektionsränder und Untersuchung in allen Dimensionen | 5 | D | ++ |
| ➤ Makroskopische Dokumentation der Gewebescheiben durch Präparate-radiographie, Photodokumentation oder Diagramm | 5 | D | + |

Aufarbeitung bei Mastektomie

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LoE / GR

- **Sampling der Resektionsränder**
 - Hautränder tumornah, mind. 2 Richtungen
 - dorsaler Rand
 - weitere Ränder, wenn knapp (< 1 cm)
- **Beachtung der Weichgewebsränder bei hautsparender Mastektomie**
- **Sampling von nicht involvierten Quadranten, Haut über Tumor, Mamille und retroareoläre Region**
- **Ausgedehntere Probenentnahme bei prophylaktischer Mastektomie (BRCA-1 pos. Patienten)**

5 D ++

5 D ++

5 D ++

5 D ++

Befundung beim invasiven Karzinom

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| | Oxford LoE / GR | | AGO |
|---|--------------------|---|-----|
| ➤ Tumortyp (WHO). Differenzierungsgrad (UICC). Tumorgroße (invasiv and extensives in situ Carcinom). pT (UICC). | 3b | C | ++ |
| ➤ Randsituation, makroskopisch alle Ränder und histologisch die nächsten <1cm. Min. Sicherheitsabstand und Topographie davon. R-Klassifikation nach TNM. | 3b | C | ++ |
| ➤ EIC (wenn vorhanden). Multifokalität (wenn vorhanden). Angioinvasion (L0, L1 bzw. V0, V1). | 5 | D | ++ |
| ➤ Anzahl untersuchter axillärer Lymphknoten, Anzahl und Größe von Lymphknotenmetastasen. Perinodale Invasion. pN (UICC). | 3b | B | ++ |
| ➤ ER-, PgR-, HER2-Status | 3b | C | ++ |
| ➤ Ki-67 (zur Objektivierung und Absicherung des Gradings) | 3b | B | + |

Evaluation nach neoadjuvanter Chemotherapie

| | Oxford LoE | / GR | AGO |
|---|---------------|----------|------------|
| ➤ Identifikation des Tumorbetts, sonst ypTX | 4 | D | ++ |
| ➤ Angabe der Tumorgröße (max. Tumorbettgröße mit vitalem, invasiven Ca.) | 4 | D | ++ |
| ➤ Tumorregressionsgrad nach Miller-Payne (2003), Symmans (2007) oder Sinn (1994) Sataloff or Chevallier (1993) | 4 | D | + |
| ➤ pCR definiert als Fehlen invasiven Karzinoms und DCIS sowie Abwesenheit von Gefäßinvasion und Lymphknotenmetastasen. | 2b | D | + |
| ➤ IHC zum Nachweis minimalen Residualtumors | 4 | D | +/- |
| ➤ Angabe von pTN-Status prä- und post-OP | 5 | D | ++ |

Histologische Bewertung der Tumor-Regression

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- **NSABP B-18:** pCR / pPR / NR
- **Chevallier:** Regressionsgrad, 1–4
- **Sataloff:** Zellularität (Tu + Lnn), 1–4
- **Miller-Payne:** Zellularität, Score 0–5
- **Symmans:** 6 Parameter (Tu + Lnn)
- **Sinn:** Regressionsgrad, Score 0–4

Unterschiedliche Definitionen der kompletten pathologischen Remission (pCR)

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| Author Grades of regr. | Invasive tumor | In-situ tumor | Intra- vascular | Lymph-node metas |
|--|-------------------|------------------|--------------------|---------------------|
| Chevallier 1–4 | - | - | - | - |
| Sinn 0-4 | - | - | - | +/- |
| Sataloff Cellularity 1–4 | -/+ | -/+ | -/+ | - |
| Miller-Payne Cellularity 1–5 | - | -/+ | - | - |
| Symmans 6 parameters | - | - | - | - |
| NSABP B-18 pCR / pPR / NR | - | -/+ | - | - |
| GBG / AGO-B | - | - | - | - |

ER, PgR Bestimmung

Oxford / AGO
LoE / GR

- | ➤ Immunohistochemischer Nachweis am Paraffinschnitt | 1a | A | ++ |
|---|----|---|----|
| ➤ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 1\%$) | 1a | A | ++ |
| ➤ Angabe der Färbeintensität | 4 | D | + |
| ➤ Rezeptorstatus durch RNA-Bestimmung | 2b | B | -- |
| ➤ Allred Score (0–8), Remmele Score (0–12) | 4 | D | + |
| ➤ Reevaluation am Exzidat, wenn unklarer Befund an der Stanze oder triple-negativ | 5 | D | + |
| ➤ Durchführung qualitätssichernder Maßnahmen und Beteiligung an Ringversuchen | 5 | D | ++ |

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ER/PgR Interpretation

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| Klassifikation | ASCO/CAP 2010 | Remmele-Score | Allred-Score | St Gallen Konsensus 2009 |
|---|----------------|--|---|--------------------------|
| Bewertung | Prozentualität | Färbeintensität (1-3)x Prozentualität (1-4) = max. 12 | Färbeintensität (1-3)+ Prozentualität (1-5) = max. 8 | Prozentualität |
| | | > 0 bis < 10% = 1 | > 0 bis 1% = 1 | Schwach positiv: >0-49% |
| | | 10 bis < 50% = 2 | > 1% bis 10% = 2 | |
| | | 50% bis 80% = 3 | > 10% bis 33% = 3 | Hoch positiv: = 50% |
| | | > 80% = 4 | > 33% bis 66% = 4 | |
| | | | > 66% bis 100% = 5 | |
| Positiv | Positiv = 1% | Positiv (Score) = 3 | Positiv (Score) = 3 1% mäßig gefärbt | Positiv > 0 (%) |
| Negativ | Negativ < 1% | Negativ (Score) = 2 | Negativ (Score) = 2 | Negativ 0 (%) |
| Diskrepante Positivitäts-Grenze im Vergleich zu ASCO/CAP | | 1% mindestens stark gefärbt | 1% mindestens mäßig gefärbt | >0% - <1% |
| Diskrepante Negativitäts-Grenze im Vergleich zu ASCO/CAP | | 49% schwach gefärbt; 9% mäßig gefärbt | 1% schwach gefärbt | >0% - <1% |

HER2 Bestimmung

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| | Oxford LoE / GR | / | AGO |
|---|--------------------|---|-----|
| | 1a | A | ++ |
| <ul style="list-style-type: none"> ➤ Immunohistochemie (IHC): <ul style="list-style-type: none"> - HER2 + wenn starke komplette zirkuläre Membranfärbung von >10% invasiver Zellen (3+ Färbemuster) - wenn > 10% zirkuläre, schwache/mäßige Membranfärbung oder ≤10% stark (2+ Färbemuster): ISH erforderlich (CISH, SISH, FISH) | | | |
| <ul style="list-style-type: none"> ➤ Einfarben In-Situ-Hybridisierung (ISH): <ul style="list-style-type: none"> - HER2+ wenn ≥ 6 Signale in mindestens 20 kohäsiven Zellen, negativ bei < 4 Signalen/Kern | 3a | C | ++ |
| <ul style="list-style-type: none"> ➤ Zweifarben ISH: <ul style="list-style-type: none"> - HER2+ bei Signal Ratio HER2:CEP17 ≥ 2,0 und/oder HER2-Signale ≥ 6 | 3a | C | ++ |
| <ul style="list-style-type: none"> ➤ Uneindeutiges Ergebnis (2+ IHC, ≥ 4 - < 6 HER2 Signale ISH): Retestung mit anderer Methode oder an anderem Block | 3a | C | ++ |
| <ul style="list-style-type: none"> ➤ Validierung der Immunohistochemie an Stanzbiopsien | 5 | D | ++ |
| <ul style="list-style-type: none"> ➤ Interne und externe Qualitätskontrolle | 5 | D | ++ |
| <ul style="list-style-type: none"> ➤ RNA-Messung (qtPCR, Array-Technologie) | 2b | B | -- |

HER2-Bestimmung an Stanzbiopsien

Da eine Falschpositivität an Stanzbiopsien vorkommen kann (3+), sollte vor regelmäßiger HER2-Diagnostik an Stanzbiopsien eine Validierung der Methodik durch Parallelfärbung und Vergleich mit dem Resektat vorgenommen werden. Eine vermehrte Reaktivität des Stanzgewebes äußert sich an vermehrter Hintergrundfärbung, die durch den Vergleich mit normalem duktalem Epithel abgeschätzt werden sollte.

Alternativ oder zusätzlich können alle G1 und G2 Fälle mit HER2 3+ Befund in der Stanzbiopsie durch eine ISH oder eine Parallelbestimmung am Resektat überprüft werden.

Falschpositivität ist wahrscheinlich, wenn HER+ bei G1 Tumoren der folgenden histologischen Typen : infiltrierendes ductales or lobuläres Karzinom, ER und PgR positiv, tubulär, muzinös, cribriform, denoid zystisches Karzinom (n. WHO)

Im Falle einer Diskrepanz zwischen Resektat und Stanzbiopsie sollte die Probe mit einer Überexpression einer ISH unterzogen werden. Sollte in einer der Proben eine Amplifikation sicher nachgewiesen sein, genügt das für eine eventuelle Indikationsstellung zur anti-HER2 spezifischen Therapie. Die zu erwartende Positivitätsrate liegt bei etwa 16% aller Fälle

Intrinsische Typen des Mammakarzinoms (molekulare und immunohistochemische Definitionen)

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- **Die sogenannten intrinsischen Typen (basal, luminal A/B-Typ, HER2) sind durch RNA-Expressionsprofile definiert. Es gibt zur Zeit keine allgemein akzeptierte Übertragung in Immunphänotypen, weder in Hinblick auf die notwendigen Marker noch die Schwellenwerte**
- **Unter praktischen Gesichtspunkten kann aber die Anwendung der Terminologie zur Beschreibung etablierter immunhistochemischer Untergruppen des Mammakarzinoms vertreten werden (ER/PR+ = luminal, HER2+ = HER2-Typ, triple negativ = basaler Typ)**
- **Der basale Typ weist eine 80% Überlappung mit der triple negativen Untergruppe des ductal invasiven Mammakarzinoms auf (ER <1% & PR <1% & Her2 0/1+/2+ (nicht-amplifiz., Ratio <2)**
- **Keiner der z.Zt. verfügbaren Marker (Ki-67, Grading, Recurrence Score etc.) kann zuverlässig zwischen den luminalen A and B Typen unterscheiden**
- **Auch RNA-Messungen sind zur Festlegung des intrinsischen Typs für therapeutische Zwecke nicht geeignet**

Triple-negatives Mammakarzinom

Oxford LoE: 5

GR: D

AGO: ++

- **Definition: ER <1% & PR <1% & Her2 0/1+2+ (nicht amplifiziert, Ratio Schwellenwert ≤ 2)**
- **Ausgenommen: Tumoren vom Speicheldrüsentyp, myoepitheliale Karzinome, adenoid-zystisches Ca**
- **Wiederholung der Bestimmung, wenn unklarer Befund***

*** unklarer Befund: tubuläre, lobuläre, muzinöse, kribriforme Mammakarzinome, langsam proliferierendes IDC, G2, oder wenig Tumormaterial in der Stanze, keine Expression basaler Zytokeratine**

Sentinel-Lymphknoten

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| | Oxford LoE / GR | / | AGO |
|---|--------------------|----------|------------|
| ➤ Vollständige Aufarbeitung am Paraffinschnitt mit Schnittstufen von $\leq 500 \mu\text{m}$ | 5 | D | ++ |
| ➤ Zytokeratin-Immunohistologie | | | |
| - zum Nachweis von Mikrometastasen, wenn suspekt | 2b | B | ++ |
| - routinemäßig | 5 | D | +/- |
| ➤ Schnellschnittuntersuchung | | | |
| - bei klinischer Konsequenz | 5 | D | + |
| - bei nicht zu erwartender Konsequenz (z.B. cT1 or cT2 und cN0 und BET) | 5 | D | +/- |
| ➤ Abtupfzytologie anstatt oder zusätzlich zur Schnellschnittuntersuchung | 3b | C | +/- |
| ➤ RT-PCR zum Nachweis von Metastasen | 4 | D | - |
| - OSNA | 3b | B | - |

Mutations- oder Genexpressionsanalyse

Oxford LoE: 5

GR: D

AGO: - -

- **Nur im Rahmen wissenschaftlicher Untersuchungen!**
- **TP53 (p53)**
- **PIK3CA (PI3K)**
- **PTEN**
- **Andere Genomsequenzierung**

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Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Prognostische und prädiktive Faktoren

Prognostische und prädiktive Faktoren

- **Version 2002:**
Thomssen / Harbeck
- **Versionen 2003–2013:**
**Costa / Friedrichs / Gerber / Göhring /
Harbeck / Loibl / Mundhenke / Nitz / Rody /
Schaller / Schmidt / Schmutzler /
Schneeweiss / Simon / Solomayer /
Thomssen**
- **Version 2014:**
Liedtke / Harbeck

Definition

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Ein **prognostischer Faktor*** ist ein Parameter, der zu einem interessierenden Zeitpunkt z.B. bei Erstdiagnose vorliegt und, sofern keine weitere Therapie erfolgt, mit dem krankheitsfreien oder dem Gesamtüberleben d.h. mit dem natürlichen Krankheitsverlauf korreliert.

Ein **prädiktiver Faktor** ist ein Parameter, der das Ansprechen auf eine bestimmte Therapie definiert.

***Im Sinne dieser Leitlinie gemeint sind Faktoren, die mit Krankheitsrezidiv assoziiert sind.**

“Low absolute risk implies low absolute benefit”

Threshold?

Karp et al SABCS 2012: cumulative leucemia/MDS after 10 yrs 0.5 %

Martin et al SABCS 2010: chronic heart failure (at ten years) in 3.5 % after TAC

Qualitätskriterien

- **Biologisches Modell**
- **Einfache und zuverlässige Bestimmung, Qualitätssicherung des Tests**
- **Prospektive Planung der statistischen Auswertung (primäres Zielkriterium)**
- **Validierung der klinischen Bedeutung nach**
 - „Oxford Level of Evidence (LoE_{Ox2001})“-Kriterien und „Grades of Recommendation (GR)“
 - modifizierte LOE Kriterien am archivierten Gewebe (LoE₂₀₀₉) und CTS-Kategorie¹⁻³ für Biomarker, deren Validierung ausschließlich an archiviertem Material erfolgt ist
- **Klinische Relevanz für Therapieentscheidung**

¹Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009

²Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011

³McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

| Category Element | A Prospective | B Prospective using archived samples | C Prospective/ observational | D Retrospective/ observational |
|---|---|--|---|--|
| Clinical trial | Prospective controlled trial (PCT) designed to address tumor marker | Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires Prospective randomized controlled trial (PRCT) | Prospective observational registry, treatment and follow-up not dictated | No prospective aspect to study |
| Patients and patient data | Prospectively enrolled, treated, and followed in PCT | Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest | Prospectively enrolled in registry, but treatment and follow-up standard of care | No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review |
| Specimen collection, processing, and archival | Specimens collected, processed, and assayed for specific marker in real time | Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion | Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion | Specimens collected, processed and archived with no prospective SOPs |
| Statistical design and analysis | Study powered to address tumor marker question | Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays | Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays | Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays |
| Validation | Result unlikely to be play of chance Although preferred, validation not required | Result more likely to be play of chance than A but less likely than C Requires one or more validation studies | Result very likely to be play of chance Requires subsequent validation studies | Result very likely to be play of chance Requires subsequent validation |

Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies

| Level of Evidence | Category | Validation studies available |
|-------------------|----------|---|
| I | A | None required |
| I | B | One or more with consistent results |
| II | B | None or inconsistent results |
| II | C | 2 or more with consistent results |
| III | C | None or 1 with consistent results or inconsistent results |
| IV–V | D | Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility |

Requirements for a Marker-Based Test to Reach Level IB Evidence

- **1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.**
- **2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.**
- **3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.**
- **4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.**

Prognosefaktoren I – Primäres Mammakarzinom

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| Faktor | LoE _{Ox2001} | GR | AGO |
|---|-----------------------|----|-----|
| ➤ Tumorgroße | 1a | A | ++ |
| ➤ Lymphknotenstatus | 1a | A | ++ |
| ➤ Vorliegen von Fernmetastasen | 1a | B | ++ |
| ➤ Histologischer Typ (kolloid, muzinös, tubulär etc.) | 2b | B | ++ |
| ➤ Grading (Elston&Ellis) | 2a | B | ++ |
| ➤ Alter | 2a | B | ++ |
| ➤ Einbruch in Lymph- und/oder Blutgefäße | 2b | B | + |
| ➤ pCR nach NACT* bei (HR+/G3, HER2+, TN) | 1a | A | ++ |
| ➤ BMI | 1b | B | + |

* NACT = Neoadjuvante Chemotherapie

Reproducibility

- **ER/PR discordance central vs local $\approx 20\%$ (ASCO/CAP JCO 2010)**
- **HER2 inaccurate testing suspected in approximately 20% (ASCO /CAP JCO 2007)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, pN1mi: 11% upstaged, 15% downstaged in central pathology review (Ann Oncol 2012)**
- **Consistency: 107 cases examined by 23 pathologists in 4 rounds: Grading: Kappa 0,53; LVI Kappa 0,38 (ECWGBSP, 1999) (Virchows Arch 1999)**

Prognosefaktoren II – Primäres Mammakarzinom

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Es muss betont werden, dass die *Levels of Evidence* mittels Oxford- und CTS-Kriterien nicht direkt verglichen werden können.

Die prospektiv-geplante retrospektive Validierung von Biomarkern (CTS-Level 1) kann durch eine unzureichende Anzahl von Proben aus einer klinischen Studie verzerrt werden.

Diese Gewebesammlung könnte möglicherweise nicht das Ergebnis der Gesamtstudie repräsentieren. Ein optimaler Prozentsatz von Proben einer klinischen Studie für eine optimale Biomarker-Evaluierung ist bislang nicht etabliert.*

* Simon, Paik, Hayes, J Natl Cancer Inst 101: 1446-1452, 2009

Prognosefaktoren II – Primäres Mammakarzinom

| Faktor | LoE _{Ox2001} | GR | AGO |
|--|-----------------------|----|-----|
| ➤ ER / PgR | 2a | B | + |
| ➤ HER2 (IHC, FISH) | 2b | B | + |
| ➤ ER / PgR / HER2 als Surrogatmarker für molekulare Subtypen | 2b | B | + |
| ➤ uPA / PAI (Femtelle® ELISA) [§] in N0 | 1a | A | + |
| ➤ Proliferationsmarker | | | |
| ➤ Ki-67 vor, während oder nach der Behandlung | 2b | B | + |
| ➤ Mitotic activity Index (MAI) | 1a | A | + |

[§] Validierte klinische Daten sind nur verfügbar für diesen Assay

Commercially Available Molecular Tests

| | 70 gene signature (MammaPrint®) \$ | 21 gene Recurrence score (Oncotype DX®) \$ | 8 gene signature (Endopredict®) \$ | PAM 50 (Prosigna®) \$ |
|--|---|--|---|---|
| Provider | Agendia | Genomic Health | Sividon | NanoString |
| Type of assay | 70-gene assay | 21-gene recurrence score | 11-gene assay | 50-gene assay |
| Type of tissue | fresh frozen (technical validation for FFPE available) | FFPE | FFPE | FFPE |
| Technique | Microarrays for RNA | qRT-PCR | q-RT-PCR | qRT-PCR |
| Central lab | yes | yes | no | no |
| Indication and population studied | prognostic N ₀₋₁ , <61 Jahre | prognostic N ₀₋₁ ER+ endocrine treated | prognostic (pre-) postmenopausal N ₀₋₁ ER+ HER2- endocrine treated | prognostic postmenopausal N ₀₋₁ ER+ HER2- endocrine treated |
| Clinical Validation | yes | yes | yes | yes |
| Registration | FDA clearance as "In Vitro Diagnostic Multivariate Index Assay (IVDMIA)" | Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)- accredited ref lab | CE-Mark | FDA 510(k) Clearance |

\$ Validated clinical data only available for this assay

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Commercially Available Molecular Tests

| | 70 gene signature (MammaPrint®) \$ | 21 gene Recurrence score (Oncotype DX®) \$ | 8 gene signature (Endopredict®) \$ | PAM 50 (Prosigna®) \$ |
|--|---------------------------------------|--|---------------------------------------|--|
| Prognosis after 5 yrs (late recurrences) | not separately shown | no | yes | yes |
| Predictive impact (chemotherapy benefit) | poorly validated | yes * | not shown | not shown |
| Prospective- retrospective evidence (% of recruited patients) | Multicenter validation | NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%) | ABCSG 6 (19%) ABCSG 8 (36%) | MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%) |
| Prospective evidence (pending) | MINDACT (completed) | TAILOR _X (n0, completed) RxPONDER (n1, ongoing) | - | - |

\$ Validated clinical data only available for this assay

* Trial performed before HER2 testing, HER2 positive patients may have been included

Prognosefaktoren II – Primäres Mammakarzinom

| Faktor | LoE ₂₀₀₉ | CTS | AGO |
|--|---------------------|-----|-----|
| ➤ Disseminierte Tumorzellen (DTC, im Knochenmark) | I | B | +/- |
| ➤ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®) \$ | I | B | +/- |
| ➤ Therapieentscheidungen basierte auf CTC-Phänotypen | III | C | - |
| ➤ 21-Gen-Recurrence-Score (Oncotype DX®) \$ (N0-1 ER+ HER2-, endokrin behandelt) | | | |
| ➤ N0 | I | B | + |
| ➤ N1 | II | B | +/- |
| ➤ 8-Gensignatur (EndoPredict®) \$ (postmenopausal, N0-1 ER+ HER2-, endokrin behandelt) | | | |
| ➤ N0 | I | B | + |
| ➤ N1 | II | B | +/- |
| ➤ 70-Gensignatur (MammaPrint®), N0-1 | II | C | +/- |
| ➤ PAM 50 (Prosigna®) \$ (postmenopausal, N0-1 ER+ HER2-, endokrin behandelt) | II | B | +/- |
| ➤ IHC4 (zentrale Pathologie, publizierter Algorithmus) # | I | B | +/- |

* Sollte nur bei ausgewählten Patientinnen angewandt werden, wenn alle anderen Kriterien keine Therapieentscheidung zulassen

\$ Validierte klinische Daten nur verfügbar für diesen Assay

Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

Neoadjuvante Chemotherapie

Therapieprädiktion I

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| Faktor | CTS | LoE _{Ox2001} | GR | AGO |
|--|-----|-----------------------|----|-----|
| ➤ Junges Alter | B | 1a | A | + |
| ➤ cT1 / cT2-Tumore o. N0 o. G3 | B | 1a | A | ++ |
| ➤ Negativer ER- und PgR-Status | B | 1a | A | ++ |
| ➤ Triple negative breast cancer (TNBC) | B | 1a | A | ++ |
| ➤ Positiver HER2-Status | B | 1a | A | ++ |
| ➤ Nicht-lobulärer Subtyp | B | 1a | A | + |
| ➤ Frühes klinisches Ansprechen | B | 1b | A | + |

Neoadjuvante Chemotherapie

Therapieprädiktion I

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| Faktor | LoE ₂₀₀₉ | CTS | GR | AGO |
|--|---------------------|-----|----|-----|
| ➤ PAM50 (Prosigna ^{\$}) | III | C | B | +/- |
| ➤ 70-Gensignatur (Mammaprint ^{\$}) | III | C | B | +/- |
| ➤ Ki-67 | I | B | A | + |
| ➤ Tumour infiltrating Lymphocytes | II | B | B | + |
| ➤ <i>PIK3CA</i> mutation | II | B | B | + |

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^{\$} Validierte klinische Daten nur verfügbar für diesen Assay

Prädiktive Faktoren – Endokrine Therapie

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| Faktor | LoE _{Ox2001} | GR | AGO |
|--|-----------------------|----|-----|
| ➤ Endokrine Therapie | | | |
| ➤ ER/PgR Status | 1a | A | ++ |
| ➤ IHC Färbeintensität (ER/PgR) | 1a | A | + |
| ➤ Tamoxifen | | | |
| ➤ CYP2D6 Polymorphismus | 2b | D | - |
| ➤ Ovarielle Ablation | | | |
| ➤ Menopausenstatus | 1c | A | ++ |
| ➤ Aromataseinhibitoren vs. Tamoxifen | | | |
| ➤ Menopausenstatus | 1c | A | ++ |
| ➤ ER / PgR / HER2 als Einzelmarker | 1c | A | - |
| ➤ Lobulärer Subtyp | 2b | B | + |
| ➤ Ki-67 hoch (publizierte Cutoffs >11% und >14 %) | 2b | B | +/- |
| ➤ BMI | 2b | B | +/- |

Prädiktive Faktoren – HER2 gezielte Therapie / Adjuvante Chemotherapie

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| Faktor | LoE _{Ox2001} (\$ LoE _{Ox2009}) | GR (\$ CTS) | AGO |
|---|--|----------------|-----|
| ➤ Anti-HER2-Therapie | | | |
| ➤ HER2 | 1a | A | ++ |
| ➤ Adjuvante Chemotherapie | | | |
| ➤ uPA / PAI1 (Femtelle®) ELISA \$ | 1a | A | + |
| ➤ 21-Gen-Recurrence-Score (Oncotype DX®) \$ | I \$ | B \$ | +/- |

Prognosefaktoren – Metastasiertes Mammakarzinom

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| Faktor | LoE ₂₀₀₉ | CTS | AGO |
|---|---------------------|----------------|-----|
| ➤ Zirkulierende Tumorzellen (CTC im Blut, Cell Search®) | | | |
| ➤ Prognose | I | B ^a | + |
| ➤ Therapieentscheidungen allein basiert auf dynamischen Veränderungen im Verlauf | I | A ^a | - |
| ➤ Therapieentscheidungen basiert auf CTC-Phänotypen | III | C | -* |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Läsionen mit unsicherem biologischen Potenzial (B3)

(ADH, LIN, FEA, Papillom, Radiäre
Narbe)

Läsionen mit unklarem biologischen Potenzial (B3)

- **Versionen 2005–2013:**
**Albert / Audretsch / Brunnert / Fersis /
Friedrich / Gerber / Kreipe / Nitz / Rody /
Schreer / Sinn / Thomssen**
- **Version 2014:**
Sinn / Fersis

Pathologische Berichterstellung für minimalinvasive Biopsien

B-Klassifikation*

B1 = nicht verwertbar oder ausschließlich normales Gewebe

B2 = benigne

B3 = benigne, aber mit unsicherem biologischen Potenzial

B4 = verdächtig auf Malignität

B5 = maligne

B5a = intraduktal

B5b = invasiv

B5c = unklar, ob invasiv oder in situ

B5d = nicht epithelial, metastatisch

* National Coordinating Group for Breast Screening Pathology (NHBSP), E.C.
Working Group on Breast Screening Pathology, S3-Leitlinien

B3-Läsionen

- **Läsionen mit Risiko eines assoziierten DCIS oder invasiven Ca:**
 - **Atypische duktale Hyperplasie (ADH)**
 - **Lobuläre Neoplasie (ALH und LCIS)**
 - **Flache epitheliale Atypie (FEA)**
- **Inhomogene Läsionen mit Sampling-Risiko:**
 - **Phylloides Tumor, zellreiches Fibroadenom**
 - **Papillom, wenn unvollständig entfernt**
 - **Radiäre Narbe, komplexe sklerosierende Läsion**

Management nach minimalinvasiver Biopsie

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➤ **Interdisziplinäre Konferenz: Pathologie und
Bildgebung konkordant?**

→ ja: Vorgehen gemäß histologischem Typ

3a C ++

→ nein: Offene PE

3a C ++

Atypische duktale Hyperplasie (ADH)

- Synonyme: Atypische intraduktale Epithelproliferation
- Definition: Atypische intraduktale Proliferation mit zytologischen und strukturellen Merkmalen eines gut differenzierten DCIS, wie Ausbildung starrer Brücken oder Mikropapillen, häufig gut erkennbaren Zellgrenzen und höchstens zwei ganz von atypischen Epithelproliferaten ausgefüllte Gängen. Die Summe der Durchmesser aller betroffenen Lumina in einer duktulo-lobulärer Einheit (TDLUs) nicht mehr als 2 mm. Proliferationen größer 2 mm oder mehr als zwei komplett ausgefüllte Gänge werden als DCIS (low-grade) bezeichnet.
- Indikator-/Vorläuferläsion: Ipsi- and kontralateral erhöhtes Brustkrebsrisiko: 3 – 5-fach nach 10 Jahren.
- Eine Einteilung in DIN 1 - 3 (duktales intraepitheliales Neoplasie Grad 1 - 3) ist nicht ausreichend validiert.

Brustkrebsrisiko nach atyp. Hyperplasie

Stratifizierung des Brustkrebsrisikos*

| | | |
|---------------------|-------------|-----------|
| ➤ Anzahl der Herde: | 1 | RR = 2,33 |
| | 2 | RR = 5,26 |
| | ≥ 3 | RR = 7,97 |
| ➤ Mikrokalk | vorhanden | RR = 3,21 |
| | nicht vorh. | RR = 4,21 |
| ➤ Typ | duktal | RR = 3,83 |
| | lobulär | RR = 3,67 |
| | beides | RR = 7,10 |
| ➤ Alter | < 45 | RR = 6,76 |
| | 45 – 55 | RR = 5,10 |
| | > 55 | RR = 2,67 |

*AC Degnim et al. J Clin Oncol 2007; 25: 2671-2677

Strategie nach Diagnose einer ADH

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➤ **ADH in Stanz- / Vakuumbiopsie:**

→ Offene Exzisionsbiopsie

3a C ++

→ Offene Exzisionsbiopsie verzichtbar unter
der Voraussetzung dass,

a) Herd klein (≤ 2 TDLU* in Vakuumbiopsie) und

b) Pathologische Bildgebung komplett entfernt **5a C +**

➤ **ADH im Resektionsrand:**

→ Keine Nachresektion, wenn die
Veränderung ein intraduktales oder
invasives Karzinom begleitet

3a C ++

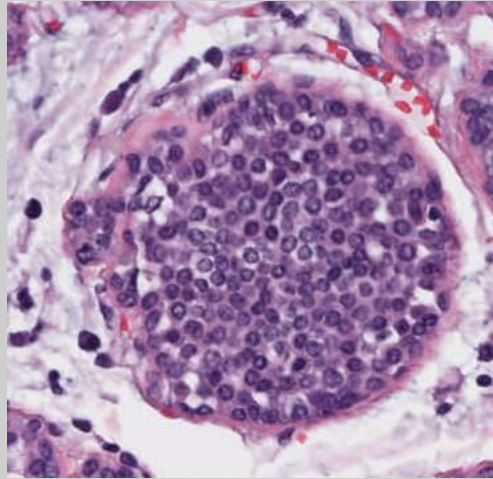
Lobuläre intraepitheliale Neoplasie (LIN)

- Beinhaltet: Atypische lobuläre Hyperplasia (ALH), lobuläres Carcinoma in situ (LCIS/CLIS)
- Eine Einteilung in LIN 1 - 3 ist prognostisch nicht ausreichend validiert
- Pleomorphe LIN und LIN mit Nekrose werden als maligne klassifiziert → **B5a**
- Indikator-/Vorläufer-Läsion:
Ipsi- und kontralateral erhöhtes Brustkrebsrisiko: 7-fach nach 10 Jahren

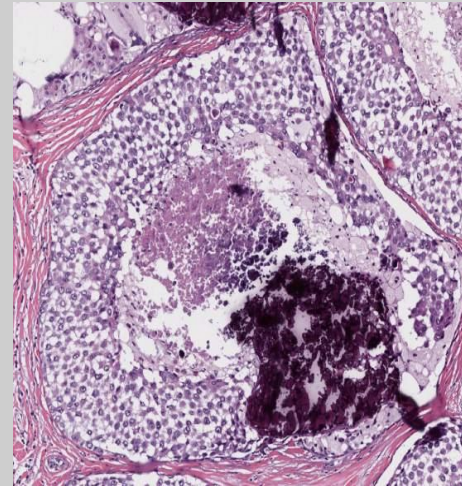
Formen des LCIS

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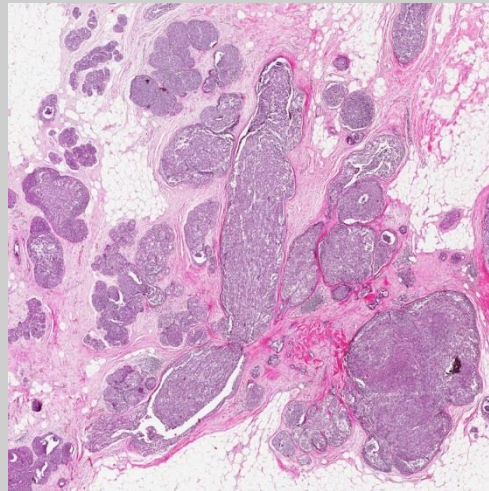
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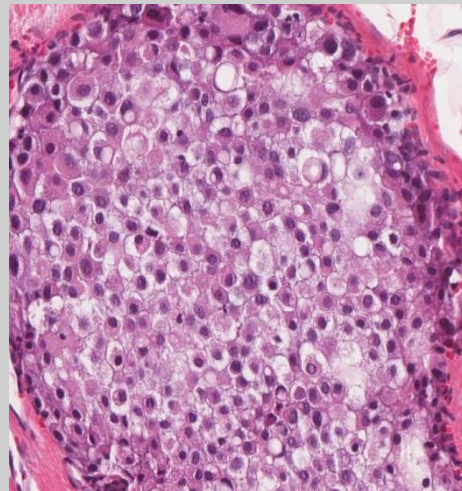
Klass. LIN



LIN mit Komedonekrose



Floride LIN



Pleomorphe LIN

LIN mit hohem Risiko

- Pleomorphes LCIS: höhergradige zelluläre Atypien, häufig Befall der Gänge mit Komedotyp-Nekrosen und Mikroverkalkungen
- Florides LCIS: Befall zahlreicher Läppchen mit maximaler Distension bis Konfluenz und Übergreifen auf Duktuli und benachbarter TDLU
- Mikroinvasion bei ILC*:
 - klass. LCIS: n=11
 - florides LCIS: n=4
 - pleomorphes LCIS: n=1

Strategie nach Diagnose einer LIN

**Oxford / AGO
LoE / GR**

➤ **LIN in Stanz- / Vakuumbiopsie:**

→ Offene Exzisionsbiopsie bei pleomorpher LIN, florider LIN, LIN mit Komoedotypnekrosen, oder wenn Befund nach Korrelation mit der Bildgebung diskordant ist.

2b C ++

➤ **LIN am Resektionsrand von BET:**

→ Keine Nachresektion

2a C ++

➤ **Ausnahmen:**

- a) pleomorphe, floride oder LIN mit Nekrosen
- b) bildgebende Veränderung wurde nicht entfernt

→ Komplette Resektion

5 D ++

Flache epitheliale Atypie (FEA)

- Synonym: Kolumnarzellhyperplasie mit Atypien, Kolumnarzellmetaplasie mit Atypien
- Differenzialdiagnose:
 - ADH unterscheidet sich durch in das Ganglumen hineinreichende oder ausfüllende Epithelproliferate mit kribriformer oder mikropapillärer Architektur → **B3**
 - DCIS vom Clinging-Typ (clinging carcinoma G2/G3) muss als intraduktales Karzinom eingestuft werden → **B5a**
- Markerläsion:

FEA ist häufig mit Mikrokalk assoziiert und es besteht ein Zusammenhang mit dem Auftreten einer FEA und der Entdeckung von ADH und DCIS. Die Korrelation des pathologischen Befundes mit der Bildgebung ist obligatorisch.

Strategie nach Diagnose einer FEA

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LoE / GR**

➤ **FEA in der Stanz- / Vakuumbiopsie:**

→ Offene Biopsie

3b C +

→ Auf offene Biopsie kann verzichtet werden

unter der Voraussetzung, dass:

kleinherdiger Befund (≤ 2 TDLU* in Vakuumbiopsie)

und vollständige Entfernung des auffälligen

Bildgebungsbefundes

5a C +

➤ **FEA im Resektionsrand nach Exzisionsbiopsie:**

3b C ++

→ Keine Nachresektion, außer

bei verbliebenem mammographischem Korrelat

* TDLU = terminale ductulolobuläre Einheit

Papillom

- Beinhaltet: Zentrales Milchgangspapillom, Papillom der großen Ausführungsgänge (B3), Papillom mit Atypien
- Abzugrenzen von peripheren Papillomen, von den TDLUs ausgehend, ≤ 2 mm, gelegentlich multipel
- Abzugrenzen vom Papillom mit DCIS, vom intraduktalen papillären Karzinom und gekapselten papillären Karzinom
- Indikator-Läsion:
Assoziation mit in situ oder invasiven Karzinomen (10%, bei atypischen Papillomen bis zu 20%), erhöhtes ipsilaterales Karzinomrisiko (4.6% bis zu 13% bei atypischen Papillomen)

Vorgehen nach Diagnose eines zentralen Papilloms

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- Papillom in Stanz- / Vakuumbiopsie:
→ Offene Biopsie

3a C ++

- Papillom am Rand von Resektaten:
→ Keine verfügbaren Studiendaten

Radiäre sklerosierende Läsion

- Benigne pseudoinfiltrierende Läsion mit zentralem fibroelastischem Kern und radiärem Aufbau.
- Beinhaltet:
 - radiäre Narbe
 - komplexe sklerosierende Läsion (> 1 cm)
- Zusätzlicher Risikofaktor bei Pat. mit benignen Epithelhyperplasien (proliferierender Mastopathie)
- Risiko für Upgrade in offener PE nach Diagnose einer radiär-sklerosierenden Läsion in der Stanzbiopsie: 8.3% (79/948)*

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Vorgehen bei radiärer Narbe, komplexer sklerosierender Läsion (CSL)

**Oxford / AGO
LoE / GR**

➤ **Radiäre Narbe / CSL in der Stanz- / Vakuumbiopsie:**

→ Offene Biopsie

3b C +

→ Auf offene Biopsie kann verzichtet werden
wenn Läsion klein und in der Vakuumbiopsie
bereits vollständig enthalten

5a C +

➤ **Radiäre Narbe / CSL im Resektionsrand
nach Exzisionsbiopsie:**

3b C ++

→ Keine Nachresektion

Brustkrebs-Früherkennung: Follow-up nach B3-Läsionen für Frauen im Alter zwischen 50 und 69 Jahren

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FEA, Papillom ohne Atypien, RN, CSL

➤ **Screening-Mammographie** **5 C ++**

LIN

➤ **Kurative Mammographie (12 Monate)** **3a C ++**

ADH

➤ **Kurative Mammographie (12 Monate)** **3a C ++**

➤ **Frauen mit LIN und ADH
sind über ihr persönlich erhöhtes
Brustkrebsrisiko zu informieren** **3a C ++**

Präventive Medikamentenbehandlung für Frauen mit erhöhtem Brustkrebsrisiko (einschließlich Frauen nach LIN und ADH)

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- **Tamoxifen für Frauen > 35 Jahre –
Reduktion von DCIS
und invasivem Karzinom**
- **Raloxifen für postmenopausale Frauen –
Reduktion nur von invasivem Karzinom**
- **Aromataseinhibitor für postmenopausale
Frauen**

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1a A +*

1b A +*

5 D +/-**

Eine präventive Medikamentenbehandlung sollte nur nach ausführlicher individueller Beratung angeboten werden: Der Netto-Benefit ist stark abhängig vom Risikostatus, Lebensalter und vorbestehenden Risiken für Nebenwirkungen.

Outcome präventiver Medikamentenbehandlung (1)

NSABP-P1 Study, update 2005

| | Hormon Rate/ 1000VE | Tamoxifen Rate/ 1000VE | RR | 95%CI |
|--|---------------------------|---------------------------|-------------|------------------|
| Alle Frauen | 629 | 359 | 0.57 | 0.46-0.70 |
| Mit hohem LGS | 598 | 341 | 0.58 | 0.46-0.72 |
| Mit LIN | 11.70 | 6.27 | 0.54 | 0.27-1.02 |
| wo ADH | 5.87 | 3.69 | 0.63 | 0.50-0.78 |
| Mit ADH | 10.42 | 2.55 | 0.25 | 0.10-0.52 |
| 5-Jahresrisiko < 2% | 4.77 | 3.18 | 0.67 | 0.43-1.01 |
| 5-Jahresrisiko > 5% | 11.98 | 5.15 | 0.43 | 0.28-0.64 |
| Eine Verwandte 1. Grades | 6.47 | 3.48 | 0.54 | 0.34-0.83 |
| Mehr als drei Verwandte 1. Grades | 11.24 | 5.48 | 0.49 | 0.16-1.34 |
| Frakturen | 2.88 | 1.97 | 0.91 | 0.51-0.92 |
| Endometriumkarzinom | 0.68 | 2.24 | 3.28 | 1.87-6.03 |

Angebote nur für Frauen
mit erhöhtem
Brustkrebsrisiko:

- mit LIN
- mit ADH
- mit genetischer Belastung

NSABP-P2 Study, STAR trial 2006

| | Tamoxifen Rate / 1000VE | Raloxifen Rate/ 1000VE | RR | 95%CI |
|--|----------------------------|---------------------------|-------------|------------------|
| Alle Frauen | 430 | 441 | 1.02 | 0.82-1.28 |
| Mit hohem LIN | 376 | 389 | 1.03 | 0.81-1.33 |
| nur LIN | 9.88 | 9.61 | 0.98 | 0.83-1.63 |
| Mit hohem ADH | 4.06 | 4.03 | 0.99 | 0.76-1.28 |
| nur ADH | 5.21 | 5.81 | 1.12 | 0.72-1.74 |
| 5-Jahresrisiko < 3% | 2.08 | 2.83 | 1.40 | 0.87-2.28 |
| 5-Jahresrisiko > 5% | 6.77 | 7.35 | 1.09 | 0.78-1.52 |
| Eine Verwandte 1. Grades | 4.99 | 5.18 | 1.04 | 0.83-1.55 |
| Mehr als zwei Verwandte 1. Grades | 5.16 | 5.00 | 0.97 | 0.63-1.56 |
| Endometriumkarzinom | 2.00 | 1.25 | 0.62 | 0.35-1.08 |
| Thromboembolien | 3.71 | 2.61 | 0.70 | 0.54-0.91 |
| Knochenentwicklung | 1.230 | 9.72 | 0.79 | 0.68-0.92 |

Sollte Frauen nicht
angeboten werden:

- mit moderatem Risiko nach dem 50. Lebensjahr
- mit erhöhtem Thromboembolierisiko

Outcome präventiver Medikamentenbehandlung (2)

**Risks and Benefits with long-term Tamoxifen use compared with placebo:
results from the IBIS-I Trial 96 months median follow-up
(Cuzick J et al J Natl Cancer Inst 2007:272-282)**

| | RR | 95% CI | AR je 1000* | NNT / NNH** |
|---|-------------|------------------|----------------|-------------|
| Brustkrebsinzidenz | 0.73 | 0.58-0.91 | 15 | 68 |
| Invasives Karzinom | 0.74 | 0.58-0.94 | 12 | 81 |
| Thromboembolie | 1.72 | 1.27-2.36 | 14 | 73 |
| Tiefe Beinvenenthrombose | 1.84 | 1.21-2.82 | 9 | 115 |
| Kopfschmerzen | 0.93 | 0.87-0.99 | 25 | 39 |
| Gynäkologische-/ vasomotorische Symptome | 1.08 | 1.06-1.10 | 64 | 16 |
| Brustbeschwerden | 0.77 | 0.70-0.84 | 58 | 17 |

Risikokommunikation

AR*: Absolutes Risiko je 1000 Frauen. NNT/NNH = number needed to treat oder
number needed to harm: Ausgewiesen sind nur statistisch signifikante Daten über den
Follow-up-Zeitraum von 96 Monaten.**

**Die Datenberechnung erfolgte von den Leitlinienautoren Visvanathan K et al. JCO
2009;27:3235-3258.**

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Duktales Carcinoma in situ (DCIS)

START

Duktales Carcinoma in situ (DCIS)

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- **Version 2002:**
Gerber
- **Versionen 2003–2013:**
**Audretsch / Brunnert / Costa / Fersis /
Friedrich / Hanf / Junkermann / Lux
/Maass / Möbus / Nitz / Oberhoff / Scharl /
Souchon / Thomssen**
- **Version 2014:**
Thill / Solomayer

Prätherapeutische Abklärung suspekter Läsionen (BIRADS 4)

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| | | | |
|---|-----------|----------|------------|
| ➤ Mammographie | 1b | A | ++ |
| ➤ Vergrößerungsaufnahmen von Mikroverkalkungen | 4 | C | ++ |
| ➤ Steigerung der Detektionsrate von G1/G2 DCIS durch digitale Mammographie (versus konventionell) | 2b | B | + |
| ➤ Stereotaktische Stanzbiopsie / Vakuumbiopsie (VAB) | 2b | B | ++ |
| ➤ Präparateradiographie | 2b | B | ++ |
| ➤ Setzen eines Markierungsclips in der Biopsieregion, wenn die Läsion komplett entfernt wurde | 5 | D | ++ |
| ➤ MRT zur Festlegung der Ausdehnung | 3a | C | +/- |
| ➤ Klinische Untersuchung | 5 | D | ++ |
| ➤ Feinnadelpunktion / duktale Lavage | 5 | D | - |
| ➤ Interdisziplinäre Tumorboard-Präsentation | 5 | D | ++ |

Operative Maßnahmen zur Therapie des histologisch gesicherten DCIS I

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| | Oxford / AGO LOE / GR | | |
|--|--------------------------|----------|------------|
| ➤ Exzision (drahtmarkiert) | 2b | B | ++ |
| ➤ Flankierende Drahtmarkierung bei großen Läsionen | 5 | D | + |
| ➤ Präparatradiographie | 2b | B | ++ |
| ➤ Intraoperative Sonographie (darstellbarer Befund) | 3a | C | +/- |
| ➤ Sofortige Nachresektion bei knappen Resektionsrändern (Präparateradiographie) | 1c | B | ++ |
| ➤ Intraoperative Schnellschnittdiagnostik | 5 | D | -- |
| ➤ Interdisziplinäre Tumorboard-Präsentation | 2b | C | ++ |

Offene Biopsien suspekter Läsionen (mammographische Mikrocalcificationen, suspekter US, MRI etc.) ohne präoperative Stanzbiopsie sollten vermieden werden.

Operative Maßnahmen zur Therapie des histologisch gesicherten DCIS II

| | Oxford / AGO LOE / GR | | |
|---|--------------------------|----------|------------|
| ➤ Histologisch freie Resektionsränder (pR0) | 2b | C | ++ |
| ➤ Multifokalität: BET falls möglich (inkl. RT) | 2b | B | + |
| ➤ Nachresektion bei knappem Resektionsrand (≤ 2 mm im Paraffinschnitt) | 2b | C | + |
| ➤ Mastektomie* (große Läsionen; keine sicheren Ränder im Nachresektat) | 2a | B | ++ |
| ➤ SNE* | 3b | B | + |
| ➤ Mastektomie | 3b | B | + |
| ➤ DCIS beim Mann | 5 | D | + |
| ➤ BET: ≥ 5 cm oder $> 2,5$ cm + high grade/ Komedonekrosen | 3b | B | +/- |
| ➤ Axilladisektion | 2b | B | -- |

* Patientinnen mit einem tastbaren Tumor haben signifikant höhere
Wahrscheinlichkeiten für eine okkulte Invasion (26%), Multizentrizität und ein

DCIS - Prognosefaktoren für lokales und lokoregionäres Rezidiv

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| | | | |
|---|----|---|-----|
| ➤ Resektionsränder | 1a | A | ++ |
| ➤ Residualer tumorassoziierter Mikrokalk | 2b | C | ++ |
| ➤ Alter | 1a | A | ++ |
| ➤ Größe | 1a | A | ++ |
| ➤ Grading | 1a | A | ++ |
| ➤ Komedonekrose | 1a | A | ++ |
| ➤ Architektur | 2b | C | + |
| ➤ Diagnostische Methode | 1a | A | ++ |
| ➤ Fokalität | 1a | A | ++ |
| ➤ (mod.) Van Nuys Prognose Index | 2b | C | +/- |
| ➤ Palpables DCIS | 2b | C | +/- |
| ➤ Palpabel + COX-2+p16+Ki-67+ | 2b | C | +/- |
| ➤ Palpabel + ER-, HER2, +Ki-67+ | 2b | C | +/- |
| ➤ HER2-Überexpression | 1a | B | +/- |
| ➤ ER/PgR (positiv vs. negativ) | 1a | B | +/- |
| ➤ DCIS-Score | 2c | C | +/- |
| ➤ DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom | 3b | C | ++ |
| ➤ Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ) | 2b | C | - |

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DCIS Radiotherapie

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Radiotherapie nach:

| | | | |
|---|----|---|----|
| ➤ Brusterhaltender Operation (BEO) (gesamte Brust, WBI) | 1a | A | + |
| ➤ Mastektomie | 2b | B | -- |

Sonderformen der Radiotherapie:

| | | | |
|---------------------------------------|----|---|------|
| ➤ Teilbrustbestrahlung | 3a | D | -- |
| ➤ Hypofraktionierte Radiotherapie | 2b | D | +/-* |
| ➤ Boost-RT des Tumorbettes | 2b | D | -- |
| ➤ Bei Patientinnen unter 45-50 Jahren | 2b | C | +/- |

NW und Nachteile der Radiotherapie müssen gegenüber der erreichbaren Risikoreduktion abgewogen werden. Ein Verzicht auf eine Strahlentherapie nach BEO bedeutet ein erhöhtes lokales Rezidivrisiko ohne Einfluss auf das Überleben. Dieses gilt auch für Patientinnen mit günstigen prognostischen Faktoren (low-risk-Subgruppe; Level I-Evidenz).

* hierzu liegen noch keine ausreichenden Daten zur Lokalrezidivrate vor

* Analyse im Rahmen laufender Studien

Cochrane Analyse

Postoperative Radiatio

(Gesamtkollektiv mit Radiatio nach BEO)

Goodwin A, Parker S, Gherzi D, Wilcken N.

**Post-operative radiotherapy for ductal carcinoma in situ of
the breast. Cochrane Database Syst Rev. 2013 Nov
21;11:CD000563. doi: 10.1002/14651858.CD000563.pub7.**

DCIS

Postoperative Systemtherapie

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➤ Tamoxifen (nur ER+, nur BET)

1a A +

➤ AI (wenn postmenopausal und
Kontraindikationen gegen Tamoxifen)

5 D +/-

➤ Andere endokrine Optionen

5 D -

➤ Trastuzumab (nur HER2+)

5 D --

Cochrane Analyse Tamoxifen nach DCIS (Gesamtkollektiv / mit Radiatio)

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Staley H, McCallum I, Bruce J.

Postoperative tamoxifen for ductal carcinoma in situ.

**Cochrane Database Syst Rev. 2012 Oct 17;10:CD007847. doi:
10.1002/14651858.CD007847.pub2.**

Lokalrezidiv des DCIS nach Tumorektomie +/- Radiotherapie

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- **MRT (Follow-up nach LCIS in der Anamnese)**
- **Einfache Mastektomie**
- **Sekundäre Tumorektomie**
führt zu Rezidiven in bis zu 30 % der Fälle
(NSABP B17)
 - **+ Radiotherapie (falls zuvor keine RT)**

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2b B +/-

3a C +

5 D +/-

3 C ++

Prognose für invasive Rezidive scheint besser zu sein als bei primären invasiven Karzinomen. Ca. 50% der Rezidive sind invasiv.

Schlüsselpunkte

- DCIS ist eine lokalisierte Erkrankung und sollte primär mit lokalen Maßnahmen behandelt werden.
- Die Hinzunahme von Tamoxifen zur Radiotherapie reduziert das Risiko eines in situ Lokalrezidivs (LoE 1a).
- Durch eine BET ist für viele Patientinnen mit DCIS eine akzeptable lokale Kontrolle zu erreichen (LoE 1a).
- Nach BEO wird eine postoperative Strahlentherapie empfohlen (LoE 1a).
- Ein Effekt auf die Überlebenswahrscheinlichkeit ist für eine postoperative Radiotherapie (10-Jahresverlauf) bisher nicht dokumentiert worden (LoE 1a).
- Jüngeres Alter bei Diagnosestellung ist ein unabhängiger Prognosefaktor für das lokale Rezidiv (LoE 1a). Daher dürften insbesondere jüngere Patientinnen von einer lokalen Boost-Radiotherapie profitieren (LoE 2b).
- Da der läsionsfreie Randsaum mehrheitlich als starker Prognosefaktor für eine lokale Kontrolle angesehen wird, sollte eine R0-Resektion angestrebt werden (LoE 1b).
- Bisher konnte keine Subgruppe von Patientinnen identifiziert werden, welche in Bezug auf die lokale Kontrolle nicht von einer Strahlentherapie nach brusterhaltender operativer Therapie profitiert (LoE 1a).
- Eine hypofraktionierte Strahlentherapie der gesamten Brust erwies sich bisher als ebenso sicher und effektiv wie eine normofraktionierte (Standard); Ergebnisse aus laufenden Studien müssen abgewartet werden.

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Operative Therapie des Mammakarzinoms unter onkologischen Aspekten

Operative Therapie des Mammakarzinoms unter onkologischen Aspekten

➤ Versionen 2002–2013:

**Bauerfeind / Böhme / Blohmer / Costa /
Fersis / Gerber / Hanf / Janni / Junkermann/
Kaufmann / Kümmel / Nitz / Rezai / Simon /
Solomayer / Thomssen / Untch**

➤ Version 2014:

Kühn / Kümmel

Präoperative Diagnostik

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|--|----------------------|----------|------------|
| ➤ Klinische Untersuchung | 5 | D | ++ |
| ➤ Mammographie | 2b | B | ++ |
| ➤ Sonographie (Brust u. Axilla) | 2b | B | ++ |
| ➤ Minimalinvasive Biopsie** | 1c | A | + |
| ➤ MRT* | 1c | B | +/- |

* Keine Reduktion der Nachresektionsrate.

Die Möglichkeit der MRT-gestützten Biopsie ist Voraussetzung für die MRT-Untersuchung, z.B. dichtes Drüsengewebe, invasiv lobuläre Tumoren, V. a. multifokale/-zentrische Tumorausbreitung.

** Wenn klinische Untersuchung, Mammographie und Sonographie ggfs. plus MRT keine exakte Ausdehnungsbeurteilung erlauben.

Perioperatives Staging

Oxford / AGO LoE / GR

- | | | | |
|---------------------------------------|---|---|----|
| ➤ Anamnese und klinische Untersuchung | 5 | D | ++ |
|---------------------------------------|---|---|----|

Bei hohem Risiko für Fernmetastasen und / oder Symptome:

- | | | | |
|-----------------------------|---|---|---|
| ➤ Rö-Thorax | 5 | D | + |
| ➤ Lebersonographie | 5 | D | + |
| ➤ CT | 5 | D | + |
| ➤ Skelettszintigraphie | 5 | D | + |
| ➤ FDG-PET oder FDG-PET / CT | 4 | C | - |
| ➤ Ganzkörper MRT | 4 | C | - |

Stellenwert der operativen Optionen

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LoE / GR**

- **Die Gesamtüberlebensraten nach BET
(Tumorektomie + XRT) und MRM sind äquivalent** **1a A**
- **Die Gesamtüberlebensraten nach MRM und
radikaler Mastektomie sind äquivalent** **1b A**
- **Die Lokalrezidivraten nach „skin sparing
mastectomy“ (SSM) und MRM sind äquivalent** **2b B**
- **Die Erhaltung des Nippel-Areola-Komplexes
(NAC) bei NAC-fernem Tumor und tumorfreiem
retroareolärem Gewebe ist onkologisch sicher** **4b C**

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Brusterhaltende Operation

Vorgehensweise, Technische Aspekte

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| ➤ Nicht palpable Läsionen | | | |
| ➤ Bildgebend gestützte Drahtmarkierung | 2b | B | ++ |
| ➤ Radionuklidmarkierung | 2b | B | +/- |
| ➤ Präparateradiographie oder -ultraschall | 2b | B | ++ |
| ➤ Tumorfremde Resektionsränder | 2a | A | ++ |
| ➤ Sofortige Nachresektion bei randbildendem Tumor in der Präparateradiographie oder -ultraschall und/oder intraoperativer patholog. Untersuchung | 1c | B | ++ |
| ➤ Nachresektion bei Tumorausläufer bis in den Randbereich (Paraffinschnitt) | 3b | C | + |
| ➤ Stereotaktische Befundentfernung als alleinige Therapie | 4 | D | -- |
| ➤ Intraoperativer Ultraschall zur Reduktion der Nachresektionsrate | 1a | A | +/- |

Brusterhaltende Operation (BEO)

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- **Multizentrität** 2b B +/-

- **Histologisch befallene Resektions-
ränder trotz wiederholter
Nachresektion** 2b B - -

- **Inflammatorisches MaCa** 2b B - -

bei pCR nach neoadjuvanter Chemo +/-

Axilläre Lymphknotendisektion (ALND) I

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➤ Axilläre Lymphknotendisektion

- Endpunkt: Überleben (bei adäquater, multimodaler Therapie)
- Endpunkt: Staging
- Endpunkt: Lokoregionale Tumorkontrolle

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| | | |
|-----------|----------|------------|
| 3 | D | - |
| 3 | A | ++ |
| 2a | A | +/- |

➤ Axilläre Lymphknotendisektion bei:

- DCIS
- Klinisch cT1/2 cN0 (ohne vorangegangener SNB)
- SN positiv (cT1/2 cN0, < 3 SN+, BET + tangentialer Radiatio, keine alternative axilläre Radiatio, adäquate Systemtherapie)
- SN + (mic)
- SN (i+)
- SN + Mastektomie

| | | |
|-----------|----------|------------|
| 2b | B | -- |
| 1a | A | -- |
| 1a | B | +/- |
| 1b | A | - |
| 2b | B | -- |
| 1b | B | + |

Axilladisektion indiziert, aber nicht möglich

- Radiatio analog AMAROS-Studie

| | | |
|-----------------------|----------|------------|
| 1b^a | B | +/- |
|-----------------------|----------|------------|

Operative Therapie der Axilla vor und nach NACT

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LoE / GR**

| SLNB vor oder nach NACT bei cN0 | | | | | | |
|--|---------------------------------|------------------------------|---------------------|-----------------------|----------------------|------------------------|
| SLNB vor NACT | | | | 2b | B | + |
| SLNB nach NACT | | | | 3 | B | +/- |
| Weitere operative Therapie in Abhängigkeit von SLNB | | | | | | |
| cN-Status (vor Therapie) | pN-Status (vor Therapie) | cN-Status (nach Therapie) | operatives Vorgehen | | | |
| cN0 | pN0(sn) | - | nihil | 1a | A | + |
| cN0 | pN+(sn) analog ACOSOG Z11* | ycN0 | ALND | 3 | B | +/- |
| cN0 | pN+(sn) nicht analog ACOSOG* | ycN0 | ALND | 2b | B | + |
| cN+ | cN+ (CNB/FNA) | ycN0 | SNB ALND | 3 2b | B B | +/- + |
| | | ycN+ (CNB/FNA) | ALND | 2b | B | ++ |

* T1/T2, BET, 1-2 SLN pos., Tangentialfeldbestrahlung der Brust

Sentinel-Lymphknoten-Exzision (SNE)

Indikationen I

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| | 1b | A | ++ |
| ➤ Klinisch (cN0) / sonographisch neg. Axilla | | | |
| ➤ Zusätzliche FNA / Stanzbiopsie (klinisch/sonographisch suspekter axillärer Lymphknoten), um eine SNE zu ermöglichen | 2b | C | + |
| ➤ T 1-2 | 2b | A | ++ |
| ➤ T 3-4c | 3b | B | + |
| ➤ Multifokales / multizentrisches MaCa | 2b | B | + |
| ➤ DCIS | | | |
| ≥ 5 cm oder 2,5 cm + high grade (vgl. auch DCIS) | 3b | B | +/- |
| oder wenn eine Mastektomie indiziert ist | 3b | C | + |
| ➤ MaCa des Mannes | 2b | B | + |
| ➤ Bei der älteren Patientin | 3b | B | + |

Sentinel-Lymphknoten-Exzision

Indikationen II

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- **Während Schwangerschaft oder Stillzeit (keine Blaumarkierung)**
- **Nach vorausgegangener Tumorektomie**
- **Frühere „große“ Brust-Operation**
- **Ipsilaterales intramammäres Rezidiv nach vorheriger BET und vorheriger SNE (z.B. Reduktionsplastik, Mastektomie)**
- **SN entlang der A. mammaria interna**
- **Nach Axilla-Voroperation**
- **Prophylaktische bilaterale / kontralaterale Mastektomie**
- **Inflammatorisches MaCa**

| | | |
|-----------|----------|-------------|
| 3 | C | + |
| 2b | B | + |
| 3b | C | +/- |
| 4 | D | +/-* |
| 2b | B | - |
| 3b | B | +/-* |
| 3b | B | - - |
| 3b | C | +/- |

* Lymphoszintigraphie erforderlich

Operatives Vorgehen nach Neoadjuvanter Therapie

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| | | | |
|---|-----------|----------|-----------|
| ➤ Markierung der Tumorlokalisation | 5 | D | ++ |
| ➤ Operation | 2b | C | ++ |
| ➤ Freie Resektionsränder | 5 | D | ++ |
| ➤ Exzision in neuen Tumorgrenzen | 3b | C | + |

Zeitpunkt der operativen Therapie und der Bestrahlung nach Neoadjuvanter Therapie

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Operation

4 C ++

➤ Nach Leukozytennadir

(2 bis 4 Wochen nach dem letzten Chemotherapiezyklus)

Wenn Strahlentherapie nach

Mastektomie indiziert

2b B ++

➤ < 6 Wochen nach Operation

➤ Indikation entsprechend des Tumorstadiums vor neoadjuvanter Therapie (cN+, cT3/4a-d)

Operative Vorgehensweise nach Neoadjuvanter Therapie

**Oxford / AGO
LoE / GR**

Brusterhaltende Operation bei klinischem Ansprechen

➤ **Multizentrische Läsionen**

3 C +/-*

➤ **cT4a-c**

2b B +/-

➤ **Inflammatorisches Mammakarzinom (bei pCR)**

2b C +/-*

Mastektomie

➤ **Histologisch befallene Resektionsränder
trotz wiederholter Nachresektion**

2b C ++

➤ **Extensives DCIS**

5 D ++

➤ **Strahlentherapie nicht möglich**

5 D +/-

*** Studienteilnahme empfohlen**

Beginn adjuvanter Therapiemaßnahmen nach primärer Operation

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| | Oxford AGO LoE/GR | | |
|---|----------------------|---|-----|
| ➤ Zeitnaher Anschluss systemischer Therapie und adjuvanter RT nach OP | 1b | A | ++ |
| ➤ Beginn der adjuvanten Chemotherapie nach OP baldmöglichst, vor Radiotherapie | 1b | A | ++ |
| ➤ Wenn keine Chemotherapie: | | | |
| ➤ Beginn der adjuvanten RT innerhalb von 6-8 Wochen nach OP (Verzögerung des Bestrahlungsbegins um > 6-8 Wochen erhöht Risiko von Lokalrezidiven) | 2b | B | ++ |
| ➤ Beginn der endokrinen Therapie nach OP oder Chemotherapie baldmöglichst | 5 | D | ++ |
| ➤ Tamoxifen gleichzeitig mit Radiotherapie | 3b | C | + |
| ➤ AI gleichzeitig mit Radiotherapie | 2a | B | +/- |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Onkoplastische und rekonstruktive Mammachirurgie

Plastisch-rekonstruktive Aspekte nach Mastektomie

- Versionen 2002–2013:
Audretsch / Blohmer / Brunnert / Dall / Fersis / Hanf / Kümmel / Nitz / Rezai / Rody / Scharl / Thomssen
- Version 2014:
Lux / Rezai

Definition der onkoplastischen Operation

**Die onkoplastische Operation begann in
ihrer ursprünglichen Form als Kombination
der Lumpektomie oder Quadrantektomie
mit lokalen bzw. regionalen
Verschiebelappen, um die Brust so zu
erhalten und formen, dass signifikante
Deformitäten vermieden werden.**

Reihenfolge der Optionen der Brustrekonstruktion

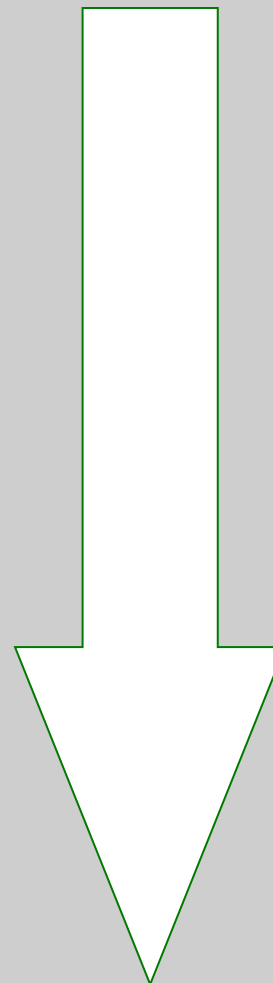
Implant

Latissimus

TRAM

Mikrochirurgie

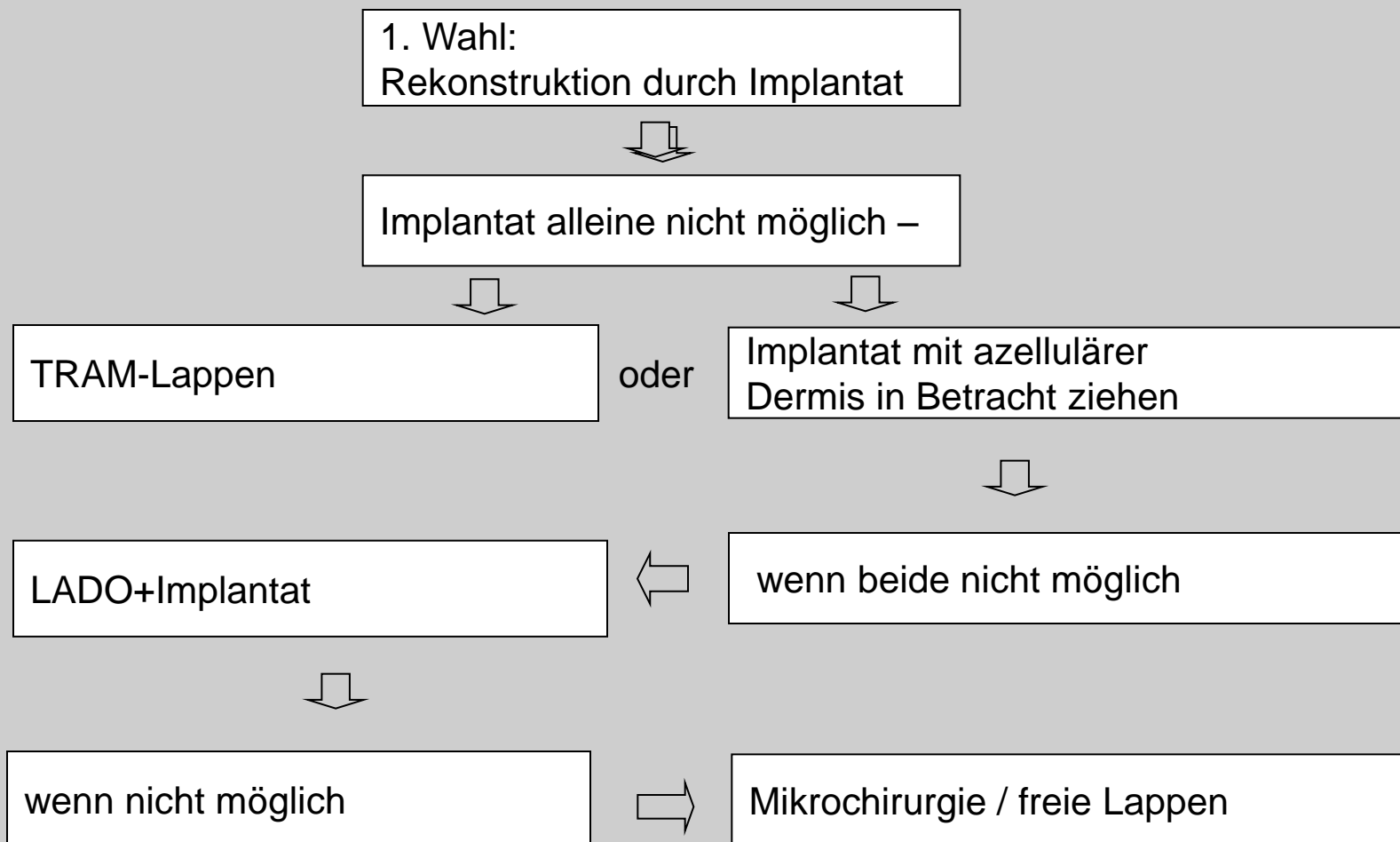
- DIEP
- SIEA
- SGAP



Algorithmus der Brustrekonstruktion

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Rekonstruktion mit Implantaten nach MX

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- **Silikongel-gefüllte Implantate sind nicht gesundheitsschädigend und haben keinen Einfluss auf das DFS und die Erkennung von Rezidiven**

| | | |
|-----------|----------|----------|
| 2a | B | + |
|-----------|----------|----------|
- **Implantat-Rekonstruktion (IR)**

| | | |
|-----------|----------|----------|
| 2a | B | + |
|-----------|----------|----------|

 - **IR ohne Strahlentherapie (RT)**

| | | |
|-----------|----------|-----------|
| 2a | B | ++ |
|-----------|----------|-----------|
 - **IR nach MX und RT**

| | | |
|-----------|----------|------------|
| 2b | B | +/- |
|-----------|----------|------------|
 - **IR vor RT / nach PBRT**

| | | |
|-----------|----------|------------|
| 2a | B | +/- |
|-----------|----------|------------|

 - **Keine Steigerung der Komplikationsrate bei Nutzung azellulärer dermaler Matrix (ADM)**

| | | |
|-----------|----------|------------|
| 3a | C | +/- |
|-----------|----------|------------|
 - **IR nach sekundärer MX (nach BET)**

| | | |
|-----------|----------|------------|
| 2a | B | +/- |
|-----------|----------|------------|
 - **Periop. verlängerte Antibiose**

| | | |
|-----------|----------|----------|
| 3b | C | + |
|-----------|----------|----------|

Radiotherapie nach Implantatrekonstruktion I

| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|--|---|---|-------------------------------|-----------------------|
| McCarthy CM PRS 2008 | Pre-or postop. radiation no significant risk factors | Independent risk factors: smoking, obesity, hypertension, age >65 39% total complication rate | 2003-2004 prospective | 1170 Exp/impl rec. |
| Berry T Ann Surg Oncol 2010 | 70,1% sucessfull | Major complic.rate 24,4% +RT 45,4% | - | Total 1037 |
| Gross E/Cowen D Cancer Radiother 2010 Breast Cancer Res Treat 2010 | 41,4 % pts. satisfied | Risk factors for failure: <u>surgeon</u> , tumor size T3 or T4, smoking, pN+, Baker 3+4 32,5 % | 37 mths. 1998-2006 | 141 |
| Whitfield GA Radiother Oncol 2009 | 70 % free of CC after 6 years | CC p < 0.001 (30 % vs. 0 %) | 51 mths. | 41/110 |
| Christante D Arch Surg 2010 | not reported | 7 % vs. 44 % p<0.001 | 2000-2008 | 302 |
| Cordeiro PG PRS 2004 | n.s. acceptable | p=0,025 CC (68% vs. 40%) | 1995-2001 | 81/606 |
| Mc Carthy PRS 2005 | 80% satisfied no Baker IV | 40% no difference 50% 1 Baker grade up 10% 2 Baker grades up | FU 23,5 mths. 1998-2002 | |
| Cordeiro PG PRS 2006 | 95% pts. satisfied | 49,3% no CC | 1992-2004 prospective | 71/410 |
| Behranwala JPRAS 2006 | 60% free of CC after 4 years | CC p<0.001 (38,6% vs. 14,1%) | 2-5 years | 44/92br |
| Benedikttson K JPRAS 2006 | Reop. n=16 free of CC after 5 years | CC p=0.01 (41,7% vs. 14,5%) | 2-5 years | 24/83 |

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Radiotherapie nach Implantatrekonstruktion II

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| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|-----------------------------------|---|--|---------------------------|---|
| Tran Tet al. 2011 | no significant differences between irradiated and non-irradiated patients | more frequently lymphedema in radiated patients | 2005-2010 retrospective | 175 (25.7% with radiotherapy), 54,8% implant based reconstruction |
| Brooks S et al. 2012 | 70,1% successfull expander/implant reconstruction | 28,4% (<50y.), 37% (>50y.) 27,5 (BMI<30), 49% (BMI>30) | 2000-2006 retrospective | 560 |
| Nava MB, Plast Reconstr Surg 2011 | not reported | Implant + RT 6.4% Expander + RT 40% | - | 257 exp vs. implant rec |
| Aristei C et al. 2012 | outcome excellent/good 57/84 | pain n=7 lympedema n=6 cutaneous toxicity n=5 subcutaneous toxicity n=19 Capsular contracture: IA 14/89 IB 47/89 II 10/89 III 11/89 IV 8/89 | 1997-2009 FU 50 months | 101 |

Radiotherapie nach Implantrekonstruktion mit Verwendung azellulärer Dermis (ADM)

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| Reference | Year | Level of Evidence/ Animal Model | RT and ADM Reconstructions (n) | Findings |
|--|------|------------------------------------|-----------------------------------|--|
| Literature review Bindingnavele et al. ²⁹ | 2007 | III | TE/I (5) | Irradiated ADM versus nonirradiated cohort demonstrated a 20% vs. 10.7% overall complication rate and 20% versus 0 expander loss rate at 10-mo follow-up |
| Breuing and Colwell ³⁰ | 2007 | III | TE/I (10) | One (10%) irradiated expander was lost compared with none in the nonirradiated cohort; 85% expander fill volume at initial surgery |
| Spear et al. ³¹ | 2008 | III | TE/I or A (11) | Radiation leads to 11-fold increase in complication rate of HADM patients with PMRT; highly select patients with prior BCT (n = 4) developed no complications |
| Nahabedian ³² | 2009 | III | TE/I (23) | Higher incidence of infection (8.7% vs. 3.9%), incisional dehiscence (13% vs. 1.3%), and seroma (13% vs. 2.6%) in HADM irradiated versus nonirradiated breasts |
| Seruya et al. ³³ | 2010 | III | TE/I or A (54) | HADM reconstruction patients receiving PMRT developed a 29.6% capsular contracture rate compared with 0.7% in nonirradiated HADM patients at an overall follow-up of 16.1 mo |
| Nguyen et al. ³⁴ | 2010 | III | TE/I (28) | For irradiated breasts, HADM use led to a significantly higher explantation rate compared with total muscle coverage (10.7% vs. 0, $p = 0.02$) |
| Israeli and Feingold ³⁵ | 2011 | III | TE/I (17) | Within HADM reconstructions, irradiated breasts had a significantly higher overall complication rate (50% vs. 3.5%, $p = 0.0005$) and expander loss rate (17.6% vs. 2.9%, $p = 0.04$) than nonirradiated breasts |
| Rawlani et al. ³⁶ | 2011 | III | TE/I (26) | HADM patients receiving PMRT compared with no radiation had nonsignificantly higher overall complication, infection, flap necrosis, and implant exposure rates |
| Salzberg et al. ³⁷ | 2011 | III | I (21) | Irradiated breasts had a fourfold higher rate of complications for HADM breast reconstructions (14.3% vs. 3.9%) |
| Colwell et al. ³⁸ | 2011 | III | I (51) | Higher overall complication rate (25.2% vs. 13.9%, $p = 0.005$); prior BCT/RT had a significantly higher complication rate (24.2%) over PMRT (16.7%) |
| Animal studies Dubin et al. ³⁹ | 2000 | 36 rat hind limbs | | No difference in HADM thickness or neovascularization when irradiated; low early fibroblast counts increasing to high late counts compared with non-irradiated controls |
| Ibrahim et al. ²⁷ | 2000 | 36 rat hind limbs | | No difference in HADM thickness when irradiated; diminished early recellularization and neovascularization increasing to normal levels by wk 12 |
| Komorowska-Timek et al. ²⁸ | 2009 | 41 rat implant capsules | | Irradiated HADM has diminished cellular invasion; however, HADM appears to decrease radiation-related inflammation and delays or diminishes pseudoepithelium formation |

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Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review. *Plast Reconstr Surg.* 2012; 130(5 Suppl 2):27S-34S.

Muskelfixation bei der primären Rekonstruktion nach Mastektomie

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|----------------------|
| ➤ Eigengewebe (z.B. Lado*) | 3b | C | +[#] |
| ➤ Azelluläre Dermis (ADM) | 2b | B | +[#] |
| ➤ Keine signifikante Steigerung der Langzeitkomplikationsrate im Vergleich zu Implantaten ohne ADM | 2b | C | |
| ➤ Geringe Rate an Kapselkontrakturen im Vergleich zum zweizeitigen Vorgehen mit Expander/Implantat ohne ADM | 2b | C | |
| ➤ Synthetische Netze | 2b | B | +[#] |

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* Latissimus dorsi Lappen

Teilnahme an Registerstudien empfohlen

Zusammenfassung der Ergebnisse von Studien mit Vergleich der Rekonstruktion mit ADM versus keine ADM

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| Author, y | Infection Rate* | | | TE Explantation | | | Seroma | | | Skin Necrosis [†] | | |
|-------------------------------------|-----------------|-------------|----------------------------|-----------------|-------------|--------------------------|-----------|-------------|---------------------------|----------------------------|-------------|--------------------------|
| | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P |
| Preminger et al, 2008 ¹⁴ | 1 (2.2) | 1 (2.2) | 0.999 | — | — | — | 3 (6.7) | 2 (4.4) | 0.645 | — | — | — |
| Sbitany et al, 2009 ¹⁵ | 4 (8) | 3 (6) | 0.99 | 4 (8) | 3 (6) | 0.99 | 3 (6) | 3 (6) | 1.0 | — | — | — |
| Nahabedian, 2009 ¹² | 22 (5.85) | 5 (5) | — | 20 (5.32) | 2 (2) | — | — | — | — | — | — | — |
| Lanier et al, 2010 ¹⁰ | 15 (28.9) | 9 (12.0) | 0.022[‡] | 10 (19.2) | 4 (5.3) | 0.02[‡] | 8 (15.4) | 5 (6.7) | 0.14 | 8 (15.4) | 4 (5.3) | 0.069 |
| Chun et al, 2010 ⁹ | 22 (8.2) | 1 (0.68) | 0.0016^{‡*} | — | — | — | 38 (14.1) | 4 (2.7) | 0.0003[‡] | 55 (20.5) | 6 (4.1) | 0.001[‡] |
| Nguyen et al, 2010 ¹³ | 11 (2.8) | 7 (3.4) | 0.291 | 6 (8) | 4 (1.6) | 0.013[‡] | — | — | — | — | — | — |
| Liu et al, 2011 ¹¹ | 13 (4.8) | 5 (2.4) | 0.172 | — | — | — | 19 (7.1) | 8 (3.9) | 0.136 | 31 (11.6) | 17 (8.3) | 0.282 |
| Present Study | 5 (16.1) | 2 (4.5) | 0.118 | 5 (16.1) | 2 (4.5) | 0.118 | 6 (19.4) | 6 (13.6) | 0.537 | 2 (6.5) | 1 (2.3) | 0.566 |

— represents not reported.
Values in bold indicate statistical significance.
*Rate of major infection, when differentiated, defined by admission for IV antibiotics or explant.
[†]Skin necrosis requiring debridement.

Hanna KR, DeGeorge BR Jr, Mericli AF, et al. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013; 70(1): 10-5.

Zusammenfassung der Charakteristika und Schlussfolgerungen von Studien mit Vergleich der Rekonstruktion mit ADM versus keine ADM

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| Author, y | No. Patients | | No. Breasts | | Conclusions |
|-------------------------------------|--------------|---------|-------------|---------|--|
| | ADM | Non-ADM | ADM | Non-ADM | |
| Preminger et al, 2008 ¹⁴ | 45 | 45 | — | — | <ul style="list-style-type: none"> • No increased morbidity with ADM use • ADM use does not facilitate increased rate of expansion |
| Sbitany et al, 2009 ¹⁵ | 50 | 50 | 92 | 84 | <ul style="list-style-type: none"> • No increased morbidity with ADM use • Faster reconstruction time with ADM use |
| Nahabedian, 2009 ¹² | 76 | 285 | 100 | 376 | <ul style="list-style-type: none"> • No increased risk of infection with ADM use • Incisional dehiscence, seroma, and infection incidence ↑ with XRT |
| Lanier et al, 2010 ¹⁰ | 52 | 75 | — | — | <ul style="list-style-type: none"> • ↑ rate of infection with ADM use in larger breasts |
| Chun et al, 2010 ⁹ | — | — | 269 | 146 | <ul style="list-style-type: none"> • ↑ rate of infection, seroma and skin necrosis with ADM use • ↑ rate of infection may be related to ↑ rate of skin necrosis and seroma |
| Nguyen et al, 2010 ¹³ | 41 | 163 | 75 | 246 | <ul style="list-style-type: none"> • ↑ rate of explantation in ADM group, possibly due to learning curve |
| Liu et al, 2011 ¹¹ | 192 | 151 | 266 | 204 | <ul style="list-style-type: none"> • ↑ overall rate of complications with ADM, increased BMI, smoking, and increased initial volume and larger implant |
| Present study | 31 | 44 | 38 | 62 | <ul style="list-style-type: none"> • No significantly increased morbidity with ADM use • Equivalent satisfaction between ADM and submuscular patients |

Hanna KR, DeGeorge BR Jr, Mericli AF, et al. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013; 70(1): 10-5.

Lipofilling

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| | | | | |
|---|--|-----------|----------|------------|
| ➤ | Lipofilling nach Implantat-basierter Rekonstruktion | 2a | B | + |
| ➤ | Lipofilling nach brusterhaltender Therapie | 4 | D | +/- |
| ➤ | Mit Stammzellen (ACS) angereicherte, autologe Fettgewebstransplantation | 5 | D | - |

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Follow-up-Ergebnisse nach Lipofilling

| | Patients (n) | Follow-up before lipofilling (months) | Local recurrence before n (%) | Follow-up after lipofilling, months (minimum– maximum) | Local recurrence after n (%) | Local recurrence after (incidence per 100 person- years) | Distant metastases (n) | Interval from lipofilling to recurrence (months) | Interval from lipofilling to metastasis (months) | Patients with free- disease survival at 5 years from surgery (%) | Patients with free-disease survival at 8 years (%) |
|-------------------------|-----------------|--|--|---|---------------------------------------|---|------------------------------|---|---|--|---|
| Rigotti et al. [20] | 137 | 23 | 4 (2.92) | 60 | 5 (3.6) | 0.72 | 9 | 20 ± 12 | 21 | 95.6 | 91.5 |
| Rietjens et al. [21] | 155 | 35.2 | – | 18.3 (6–49) | 1 (0.6) | 0.43 | 0 | 2 weeks | – | – | – |
| Petit et al. [23] | 321 | 26 | – | 26 (1–128) | 13 (4.0) | 1.87 | 13 | – | – | – | – |
| Petit et al. [22] | 513 | 39.7 | 0 (0) | 19.2 (1–107) | – (2.4) | 1.5 | 15 | – | – | – | – |
| Riggio | 60 | 56.5 | 1 (1.66) | 92.2(5–132) | 2 (3.3) | 0.43 | 4 | 47 ± 14.8 (minimum 21 – maximum 73) | 28.5 | 93.3 | 90 |

Riggio E, Bordoni D, Nava MB. Oncologic surveillance of breast cancer patients after lipofilling. Aesthetic Plast Surg. 2013; 37(4): 728-35.

Gestielte Lappen zur Rekonstruktion

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Brustrekonstruktion (BR) mit autologem Gewebe

- TRAM, Latissimus-dorsi-Lappen (können muskelsparend präpariert werden)
- Delayed-TRAM bei Risikopatientinnen
- Ipsilateral gestielte TRAM
- Radiotherapie:
 - BR nach RT
 - BR vor RT (abhängig von der Qualität der Blutversorgung des Gewebes)

3b C +

3a B +

3b A +

4 C +

3b C +/-

Freie Lappen zur Rekonstruktion

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Freier Gewebetransfer

- Freier TRAM-Lappen
- DIEP-Lappen
- SIEA-Lappen
- SGAP- / IGAP-Lappen
- Freier Grazilis-Lappen (TMG)
- Freier Lat. dorsi.-Lappen

3b C +/-

4 C +/-

4 C +/-

Vorteil:

- Freier TRAM und DIEP sind potenziell muskelsparend

Nachteile:

- Zeit- und personalintensive mikrochirurgische Techniken
- Aufwendige postoperative Überwachung
- Höhere Rate an Reoperationen
- Höhere Totalnekroserate, höhere Rate an Liponekrosen
- RT vor Rekonstruktion erhöht Rate vaskulärer Komplikationen
- Keine bessere Patientenzufriedenheit als bei dem gestielten TRAM in der multivariaten Analyse

Gestielter vs. freier Gewebetransfer

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- **Muskelsparende Techniken und sorgfältiger Verschluss der Bauchdecke führt zu niedrigen Komplikationsraten unabhängig von der verwendeten Methode** 3a A ++
- **Autologer Gewebetransfer von der Bauchdecke hat die höchste Zufriedenheitsrate in allen Patientengruppen**
- **Perforatorlappen scheinen im Verhältnis zu freien oder gestielten Lappen ein höheres Risiko für Fettgewebsnekrosen zu haben**
- **Morbidität der Spenderregion, (z.B. reduzierte Muskelfunktion) kann bei allen Lappentechniken auftreten**

Lappen-Implantat-Kombination

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Lappen-Implantat-Kombination

TRAM, LDF + Implantat

- Nach RT
- Vor RT

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4 C +

3b C +

5 D -

Vorteile:

- TRAM: bevorzugt staged Prozeduren
- Verbesserte Abdeckung des Implantates
- Geeignet zur Rekonstruktion bestrahlten Gewebes

Nachteil:

- Muskelkontraktion (Lado)

Zeitpunkt der Rekonstruktion

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3b B ++

➤ Intervallrekonstruktion

- Keine Behinderung von adjuvanten Therapien (CHT, RT)
- Nachteil: Verlust des Hautmantels

➤ Sofortrekonstruktion

3b B ++

- Bevorzugt bei partieller Mastektomie (BET)
- Obligat bei SSM/NSM
- Vermeiden des Postmastektomie-Syndroms
- Gleiche Komplikationsrate wie Intervallrekonstruktion

➤ Verzögerte Sofortrekonstruktion

(„Delayed-immediate BR“)

3b B +/-

Haut / Nipple-sparende Mastektomie (SSM/NSM) und Rekonstruktion

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LoE / GR

- **Hautsparende Mastektomie (SSM/NSM)**
 - **Sicher (gleiche Rezidivrate wie bei MX bei geeigneter Pat.-auswahl)** **2b** **B** **++**
 - **Höhere Lebensqualität für Patientin** **2b** **B** **++**
 - **Erhalt des Mamillen-Areola-Komplex (NAC) unter bestimmten Bedingungen** **2b** **B** **++**
 - **Möglich nach Mastopexie / Reduktionsplastik** **4** **C** **++**
- **Hautschnitte ⇒ verschiedene Möglichkeiten:**
 - **Periareolär („Tabaksbeutel“)(höheres Nekroserisiko)**
 - **Reduktionsschnittbild: „inverses T“ oder vertikal**
 - **Inferior-lateraler Zugang/ Inframammärfalte**
 - **Niedrigste Inzidenz von Komplikationen** **2b** **B** **+**

SSM / Nipple SM

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| Author | Cases reported | Partial skin necrosis | Local recurrence | Time period |
|---|-------------------------------------|--|---|--|
| Lanitis S et al. 2010 Ann Surg | 1104 SSM 2635 NSSM | -- | 6,2% SSM 4,2% NSSM n.s. | 1997–2009 Metaanalyse |
| Jensen JA Ann Surg Oncol 2010 | 99 | 6 % | 2,7 % | Median FU 60,2 mths |
| Yi M, Kronowitz SJ 2010 Cancer | 799 SSM 1011 CM | - | n.s. (local+syst. 6.6%) | 2000-2005 |
| KIM HJ Ann Surg 2010 | 368 SSM 152 NSSM | 9.6% NAC | 0.8% SSM 2.0% NSSM (1.3%NAC) | 07.2001-12.2006 |
| Paepke S Ann Surg 2009 | 109 SSM (96 NSM) | 1,0 % of nipple necrosis | no rec. in the nipple | 2003-2006 |
| Chen CM 2009 PRS | 115 (62 benign) | Loss of NAC: 5.2% Occ.ca. 3.5% Necrosis | -- | 1998-2008 |
| Garwood ER 2009 Ann Surg | 170 | Cohort 1: 16% Cohort 2: 11% | 0,6% | 2001-2007 |
| Yano K et al. 2007 Breast Cancer | 128 | 3,1% | 2,3% | 2001–2005 |
| Petit JY et al. 2006 Breast Cancer Res Treat | 106 NSM | 4,7% Loss of NAC | 0,9% Far from NAC | 2002–2003 |
| Gerber B et al. 2003 Ann Surg | 112 (Incl.61 NSM) | 0% | 5,4% | 1994–2000 |

Risiko-reduzierende bilaterale Mastektomie für nicht erkrankte Frauen (RRBM)

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- | | | | |
|---|----|---|------|
| ➤ RRBM verringert die Brustkrebsinzidenz | 1b | A | ++ |
| ➤ RRBM bei BRCA1/2 Mutationsträgerinnen | 2a | B | ++* |
| ➤ RRBM bei hohem Mammakarzinomrisiko (z.B. lebenslanges Risiko $\geq 30\%$ oder Risiko bei heterozygotem Erbgang $\geq 20\%$), wenn Indexpatient genet. negativ getestet wurde | 3a | C | +/-* |
| ➤ Hohes Risiko und keine Beratung in spezialisierten Zentren* | 5 | D | -- |
| ➤ Nicht direktive Beratung vor RRBM | 2b | B | ++* |
| ➤ RRBM sollte im Zusammenhang mit anderen prophylakt. Op. wie BSO gesehen werden | 2a | A | ++* |
| ➤ Weitere Notwendigkeit der Fortbildung von Ärztinnen und Ärzten in Bezug auf Möglichkeiten und Vorteile der RRBM) | 1b | A | ++ |

*Beratung, Risikoberechnung und Nachsorge in spezialisierten Zentren empfohlen

Formen der Risiko-reduzierenden bilateralen Mastektomie für nicht erkrankte Frauen (RRBM)

Oxford / AGO
LoE / GR

Die RRBM reduziert die Inzidenz von MammaCa und wahrscheinlich auch die MaCa-bedingte Mortalität

- | | | | |
|--|-----------|----------|------------|
| ➤ Einfache Mastektomie | 2b | B | + |
| ➤ RRBM mittels SSM | 2b | C | + |
| ➤ RRBM mittels s.c. Mastektomie (MAK erhaltend) | 2b | C | + |
| ➤ kontralaterale prophylaktische s.c. Mastektomie | 4 | C | +/- |

DIEP-Flap I

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| Author | Cases reported | Complete loss of flap | Lipo-necrosis | Hernias in donor region |
|--|---|-----------------------|---------------|--|
| Gill PS et al 2004 PRS | 758 | 0,5% | 15,4% | 0,7% |
| Guerra et al 2004 Ann Plast Surg | 280 | 0% | 12,5% | 2,1% |
| Nahabedian et al 2005 PRS | 110 | 2,7% | 6,4% | 2,7% |
| Blondeel PN 1999 PRS | 100 | 2% | 13% | 1% |
| De Greef C et al 2005 Ann Chir Plast Esthet | 100 | 4% | 7% | 2% |
| Garvey PB et al 2006 PRS | 96 | 0% | 17,7% | 1% 9,4% bulges |
| Xu H 2009 PRS | 113 | 3,5 % | 17,7% | 0 % hernia 0,9 % bulges (med. FU only 12,3 months!) |
| Wan DC 2010 PRS | 275 1) fTRAM 2) MS fTRAM 3) DIEP | | | 1+2)BMI<30: 0 % 1)BMI>30: 0 % 2)BMI>30: 2,8 % 3)BMI<30: 6,1 % 4)BMI>30:14,3% |

DIEP-Flap II

| Author | Cases reported | Complete loss of flap | Liponecrosis partial flap loss | Hernias/ Bulges in donor region |
|---|-------------------------|-----------------------|--------------------------------|---------------------------------|
| Munhoz AM et al 2007 Breast J (on DIEP and SSM) | 30 | 3,7% | 7,4% | 3,7% |
| Lindsey JT. 2007 PRS | 140 | 6,4% | -- | -- |
| Hofer SO et al. 2007 Ann Plast Surg | 175 | 0,6% | 8,6% | -- |
| Peeters WJ 2009 PRS | 202 | n.a. | 49% Clinical 14% US 35% | n.a. |
| Selber JC 2010 PRS | fTRAM 569 DIEP 97 | 0,2% 1,0% n.s. | 4,1% 2,1% n.s. | 1,9% 0 n.s. |

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DIEP-Flap III

| Author | Cases reported | Complete loss of flap | Liponecrosis partial flap loss | Hernias/ Bulges in donor region |
|--|-------------------|-----------------------|--------------------------------|---------------------------------|
| Garvey BP et al. PRS 2011 | 228 | n.a. | 8,3/3,3% | n.a. |
| Conroy K et al. PRAS 2011 | 3 | - | - | 3 epigastric hernia |
| Momoh AO et al. Ann PS 2011 | 217 | n.a. | n.a. | 2,3%/0% |
| Andree C. et al. Med Sci Monit 2012 | 1068 | 0,8% | n.a. | n.a. |
| Gart, M et al. J Am Coll Surg 2013 | 609 Free Flaps | 5,7% | n.a. | n.a. |

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Gestielter / freier TRAM

| Author | Reported cases | Complete loss of flap | Liponecrosis | Hernias in donor region |
|--|----------------|-----------------------|--------------|-------------------------|
| Watterson PA, Bostwick J. 1995 PRS | 556 | 0 | 10,6% | 8,8% |
| Kroll SS (f-TRAM) 2000 PRS | 279 | 0,4%(1,1%) | 15,1% | |
| Lacotte B, Lejour M 1994 Ann Chir Plast Esthet | 156 | 0 | 10% | 0 |
| Clugston PA, Maxwell GP 2000 PRS | 252 | 0 | 9,1% | 5,8% |
| Petit JY, Rietjens M 1997 Ann Chir Plast Esthet | 251 | | | 7% |
| Rezai M IGCS 2010 | 310 | 0 | 10,2% | 0,6% |
| Brunnert 2001 unpublished | 776 | 0 | 8,4% | 0,4% |
| Kim EK 2009 Ann Plast Surg | 500 | major fl. 0,2 % | 14,2% | 3% (bulges) |
| Chun YS 2010 PRS | 105 biped, | 0 | 11,4% | 2,9% |

Gestielter / freier TRAM II

| Author | Reported cases | Complete loss of flap | Liponecrosis | Hernias in donor region |
|------------------------------------|----------------|-----------------------|------------------|-------------------------|
| Momoh AO et al. Ann PS 2011 | 197 | n.a. | n.a. | 2,3%/0% |
| Garvey BP et al. PRS 2011 | 228 | n.a. | 11,3/2,8% | n.a. |

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Radiotherapie nach autologer Rekonstruktion I

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| Author | Patient satisfaction | Failure complications | Observation period | Pts. RT/CTR |
|---|---|---|--------------------|----------------------------|
| Williams JK 1997 PRS | unchanged | nature of complications changes from fat necrosis to fibrosis | 1981–1994 | 19/680 |
| Soong IS 2004 Clin Oncol (Radiol) | cosmesis 85% good to excellent | no difference | 1995–2001 | 25/-- |
| Mehta VK 2004 Breast | no problems | 10% skin desquam. 30% grade 2 erythema | 1995–2000 | 22/-- |
| Huang CJ 2006 PRS | | fat fibrosis 8% n.s. | 1997–2001 | 82/109 |
| Kronowitz SJ 2009 PRS | Radiation Therapy and BR: A critical review of the literature | | >1985 | 49 Articles reviewed |

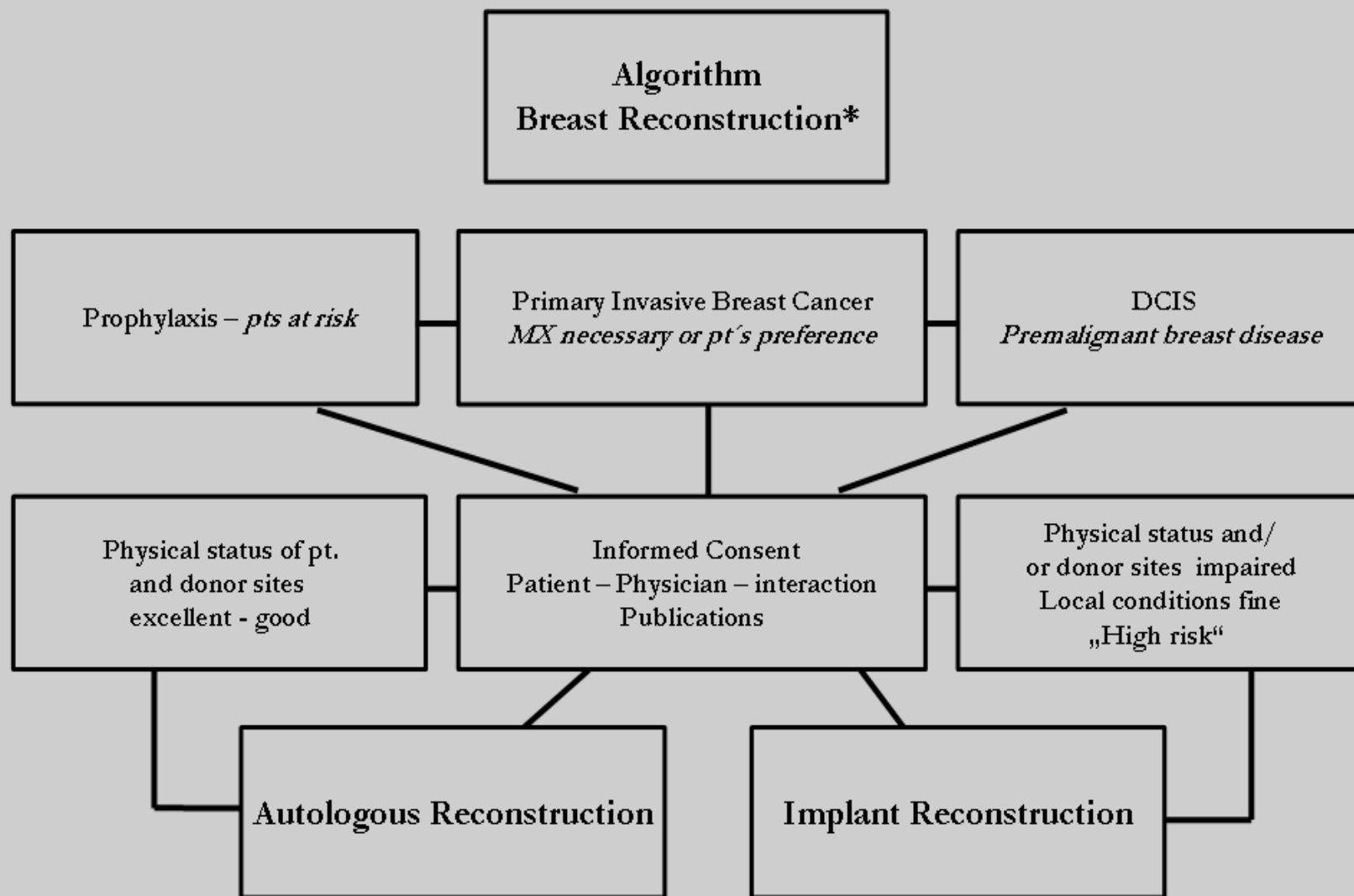
Radiotherapie nach autologer Rekonstruktion II

| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|---|----------------------|--|--------------------|------------------------------------|
| Barry M, Breast Cancer Res Treat. 2011 Meta Analysis | not reported | OR = 0.21; 95% CI, 0.1-0.4 [autologous vs. implant-based] | - | 1105 Implant vs. Autologous Recon. |

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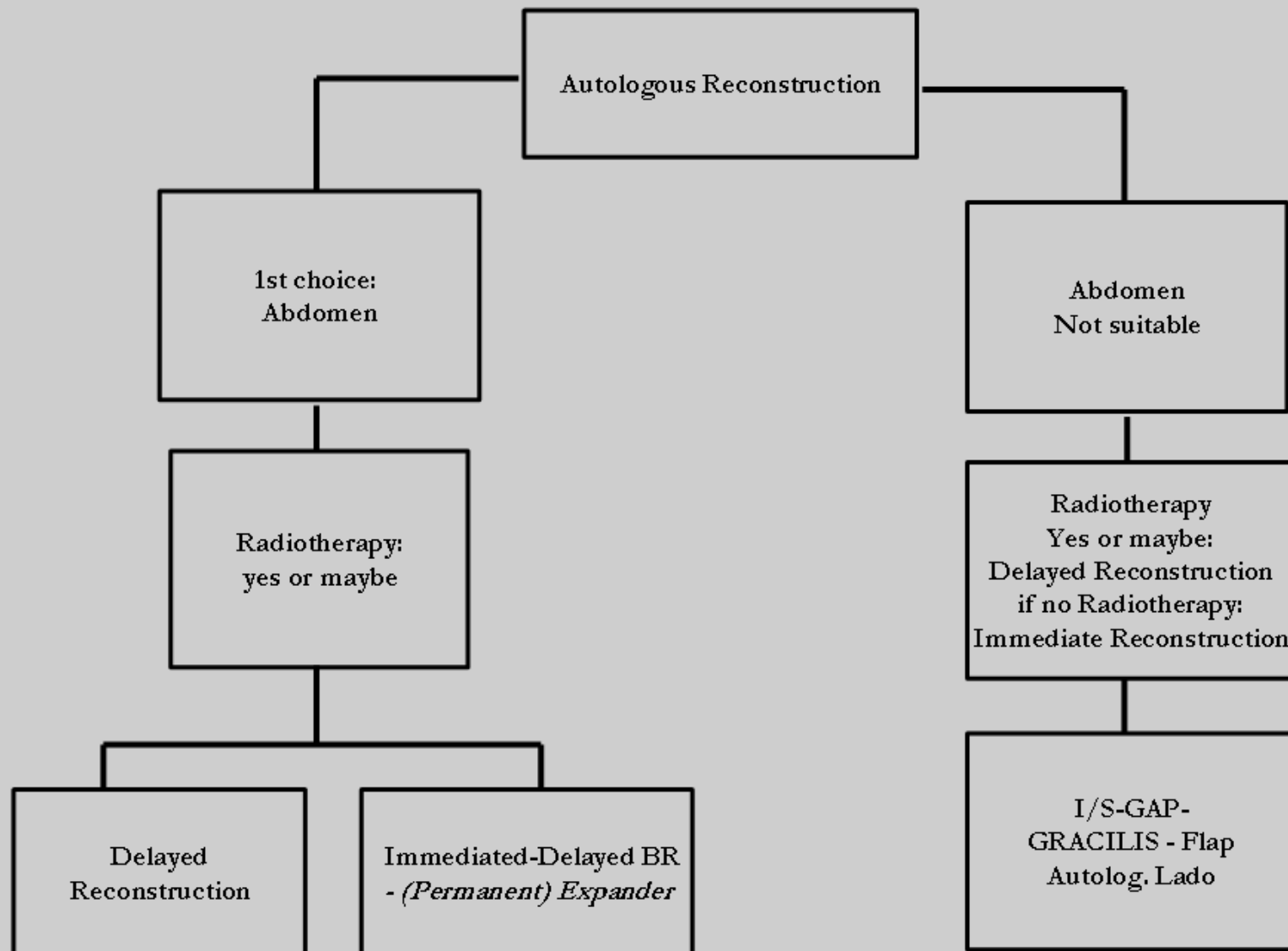
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Algorithmus der Brustrekonstruktion

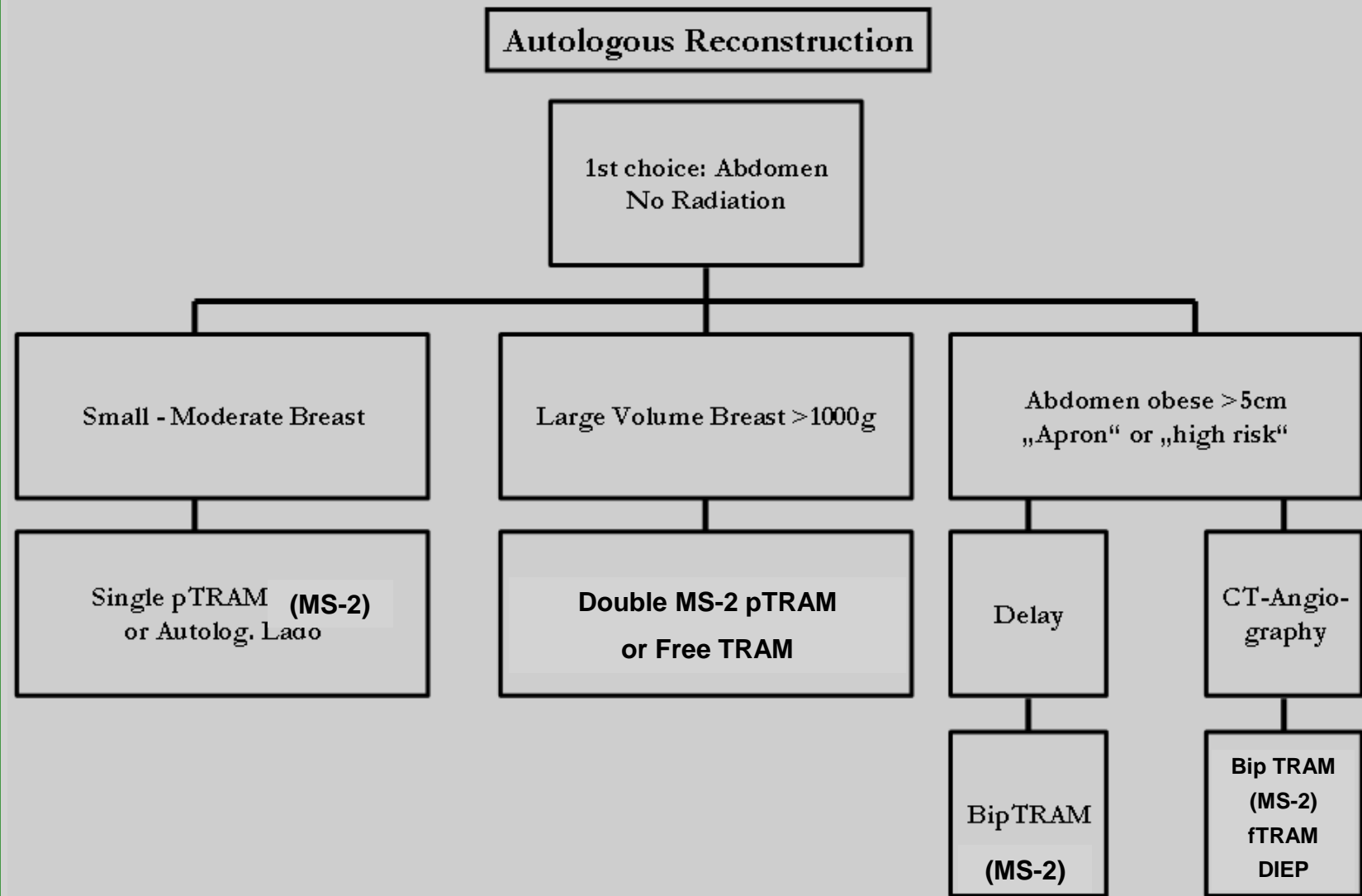


*Brunnert, K. Gyn. Prax., Band 31, 2007

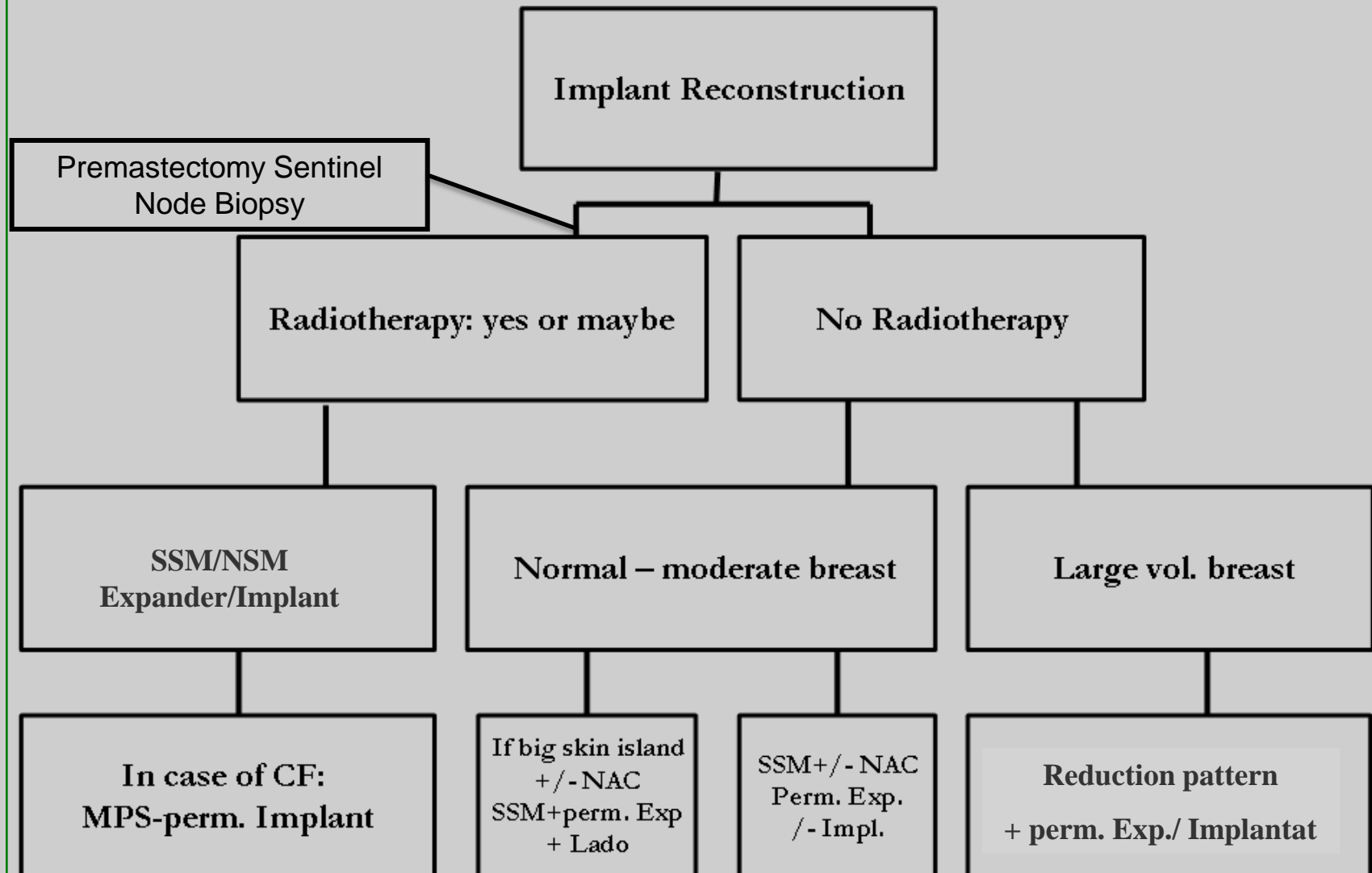
Algorithmus der autologen Brustrekonstruktion (1)



Algorithmus der autologen Brustrekonstruktion (2)



Algorithmus der Brustrekonstruktion mit Implantat



Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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START

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

➤ Versionen 2002–2013:

**Bauerfeind / Dall / Diel / Fersis /
Friedrichs / Gerber / Göring / Harbeck /
Huober / Jackisch / Lisboa / Maass /
Möbus / Müller / Oberhoff / Schaller /
Scharl / Schneeweiss / Schütz /
Solomeyer / Stickeler / Thomssen /
Untch / von Minckwitz**

➤ Version 2014: **Jackisch / Lück**

Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1

GR: A

AGO: ++

„Endokrines Ansprechen“ (früher rezeptorpositiv):

Immunhistologie (ER und / oder PgR)

| | | |
|-------------|----------------------|--------------------------------|
| 0% | pos. Zellen: | endokrin nicht sensitiv |
| ≥ 1% | pos. Zellen : | endokrin sensitiv |

| | |
|--------------------------|--------------------------|
| Status unbekannt: | endokrin sensitiv |
|--------------------------|--------------------------|

Adjuvante endokrine Therapie

Bestimmung des Menopausenstatus

Oxford / AGO
LoE / GR

Bestimmung des Menopausenstatus:

- Menstruationsanamnese +
- FSH, E2 ++

Überprüfung der ovariellen Reservekapazität (nach Chemotherapie)

- | | | | |
|-------------------------------|----|---|-----|
| ➤ Anti-Müllerian Faktor (AMH) | 3b | B | +/- |
| ➤ Follikelanzahl | 3b | B | +/- |

Adjuvante endokrine Therapie für prämenopausale Patientinnen

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LoE / GR

Standardtherapie für rezeptorpositive Tumoren:

- | | | | |
|---|-----------|----------|-----------|
| ➤ Endokrine Therapie | 1a | A | ++ |
| ➤ Chemo-endokrine Therapie (abhängig vom individuellen Risiko und dem Grad der ER/PgR Expression) | 1a | A | ++ |

Adjuvante endokrine Therapie postmenopausaler Patientinnen

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- **Endokrin sensitiv & fraglich sensitiv:
endokrine Therapie**
- **Endokrine Therapie sequentiell
nach einer Chemotherapie**
- **Nicht endokrin sensitiv:
keine endokrine Therapie**

1a A ++

2b C ++

1a A ++

Generelle Prinzipien der adjuvanten endokrinen Therapie

AGO ++

- **Therapiedauer bis zu 10 Jahren nach individueller Nutzen-Risiko-Abwägung, insbesondere bei erhöhtem Risiko (z.B. N+)**
 - **Prämenopausal: Nach 5 Jahren Tam: EAT mit Tamoxifen**
 - **Postmenopausal: Nach 5 Jahren Tam: EAT mit Tam oder AI**
- **Dauer, Wahl & Sequenz von AI oder Tam hängt v.a. von Menopausenstatus und Nebenwirkungen ab**
- **Wechsel auf eine andere endokrine Therapie (Tam oder AI) ist besser als zu stoppen**
- **AI als erste Therapie vor allem bei Hochrisiko- und lobulären Karzinomen**
- **Bislang keine Evidenz für AI > 5 Jahre**

Dauer der adjuvanten endokrinen Therapie bei prämenopausalen Patientinnen

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| | | Oxford / AGO LoE / GR | | |
|---|-------------------|--------------------------|---|-----|
| Tamoxifen* | 5 (vs. kürzer) J. | 1a | A | ++ |
| Tamoxifen* | 10 (vs. 5) Jahre | 1b | A | ++ |
| GnRH-Analoga** | 2–5 Jahre | 1b | A | ++ |
| Amenorrhoeinduktion nach CT durch GnRH-Analoga | | 2b | D | +/- |

* Behandlung solange tolerabel und prämenopausal **LoE 2b**

**Prognose der Erkrankung nach GnRHa-Therapie (≥ 2 Jahre) ist
unabhängig von der Ovarialfunktion (funktionell / nicht
funktionell)

Adjuvante (Chemo-)Endokrine Therapie bei prämenopausalen Patientinnen

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➤ Hohes oder mittleres Risiko

- | | | | |
|-----------------------|----|---|-----|
| ➤ Chemo → Tam | 1a | A | ++ |
| ➤ Chemo → Tam + GnRHa | 1a | B | +/- |
| ➤ < 40 Jahre | 3a | C | - |

➤ Niedriges oder mittleres Risiko

- | | | | |
|--|----|---|----|
| ➤ Tam allein | 1a | A | ++ |
| ➤ Tam + GnRHa | 1a | B | + |
| ➤ GnRHa allein (nur bei Kontra- indikationen gegen Tam) | 1a | B | + |

Adjuvante endokrine Therapie mit Aromatasehemmer bei prämenopausalen Patientinnen

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| | | | |
|---|-----------|----------|------------|
| ➤ GnRHa + AI | 1b | B | - |
| ➤ Falls relevante Kontraindik. gegen Tam | 5 | D | +/- |
| ➤ AI allein | 1c | A | -- |
| ➤ AI nach GnRHa (induzierte Amenorrhoe) | 5 | D | -- |
| ➤ “Upfront“-AI bei Patientinnen mit chemotherapieinduzierter Amenorrhoe (CIA, TIA) | 4 | C | -- |
| ➤ EAT bei nach 5 J. Tam sicher post- menopausalen Pat. | 2b | B | + |

Prophylaxe der ovariellen Funktion und Fertilitätserhaltung bei prämenopausalen Patientinnen mit adjuvanter Chemotherapie (CT)

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CT + GnRHa

(GnRHa Applikation > 2 Wochen vor Chemotherapie)

➤ HR+

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1b B -

➤ HR-

1b B -

1b B -

Beeinflussung des Chemoeffektes nicht ausgeschlossen!

➤ Beratung über Fertilitätserhaltung

4 C +

➤ Fertilitätserhalt mit assist. reprod. Therapie

4 C +

Kontrazeptive Möglichkeiten für Frauen nach Brustkrebs

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| | | | |
|---|---|---|-----|
| ➤ Barriere-Methoden | 5 | D | + |
| ➤ Sterilisation (Tubenligatur / Vasektomie) | 5 | D | + |
| ➤ Nicht-hormonelle intrauterine devices (IUDs) | 5 | D | + |
| ➤ Levonorgestrel-releasing IUDs | 5 | D | - |
| ➤ Entfernung bei Erstdiagnose | 4 | D | +/- |
| ➤ Timing-Methoden | 5 | D | - |
| ➤ Ausschließl. Progesteron-Kontrazeptiva (oral / im) | 5 | D | - |
| ➤ Komb. orale Kontrazeptiva | 5 | D | - |

Pat. nach Brustkrebs werden in Studien nicht berücksichtigt, östrogenfreie devices erhöhen nicht das Brustkrebsrisiko

Adjuvante Tamoxifen / Aromataseinhibitoren (AI) Behandlung bei postmenopausalen Patientinnen

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- **AI für 5 Jahre**
 - **v.a. bei lobulär-inv. Karzinomen**

| | | |
|-----------|----------|----------|
| 1a | A | + |
| 2b | B | + |
- **Sequentielle Therapie für 5 Jahre**

| | | |
|--|--|-----------|
| | | ++ |
|--|--|-----------|

 - **Tam gefolgt von AI**

| | | |
|-----------|----------|--|
| 1a | A | |
|-----------|----------|--|
 - **AI* gefolgt von Tam**

| | | |
|-----------|----------|--|
| 1b | C | |
|-----------|----------|--|

Präferenz bei N+
- **Tamoxifen 20 mg/d für 5-10 Jahre**

| | | |
|-----------|----------|-----------|
| 1a | A | ++ |
|-----------|----------|-----------|

***Derzeit Daten nur für Letrozol verfügbar**

Endokrine Therapie nach Tamoxifen bei postmenopausalen Patientinnen

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Nach 5 Jahren Tamoxifen (Erweiterte adjuvante Therapie = EAT)

➤ AI 3–5 Jahre

- Nodal-positive Erkrankung
- Langes Tamoxifen-freies Intervall

EAT mit AI denkbar auch bei Pat., die unter 5 Jahre
Tam postmenopausal geworden sind

➤ Fortsetzung Tam bis zu insg. 10 Jahre

1b A ++

2b B ++

2b B +

1a A ++

Ovarian Function Preservation – Comparison of Randomized Trials

| | ZORO | PROMISE | Munster et al. - US |
|--|--|--|---|
| Patient number | 60 (60 HR-) | 281 (50 HR-) | 49 (13 HR-) of 124 |
| Age median | 38 years | 39 years | 39 years |
| Treatment | goserelin | triptorelin | triptorelin |
| Start of treatment | >2 weeks prior to cht | >1 week prior to cht | > 1 week prior to cht |
| Primary Endpoint | menstruation at month 6 after chemotherapy | rate of early menopause at month 12 after chemotherapy | menstruation rate within 2 years after cht |
| Primary objective | to detect 30% absolute increase of menstruation rate | to detect at least 20% absolute reduction in early menopause | to detect 20% difference in amenorrhea rate - from 10% to 30% |
| Multivariable analysis | age as only independent predictive factor | treatment as only independent predictive factor | n.d. |
| Resumption of menses at month 12 in HR- cohort | 83% with LHRH vs. 80% w/o | 93% with LHRHa vs. 74% w/o | 74% with LHRH vs. 68% w/o |
| Median time to restoration of menstruation (months) | 6.1 with LHRHa vs. 6.8 w/o; p=0.30 | not reached with LHRH vs. 6.7 w/o; p=0.07 | 5.8 with LHRH vs. 5.0 w/o; p=0.58 |
| Cyclophosphamide dose | 4600 vs. 4700mg | 4080 vs. 4008 mg | n.r. |

Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Metaanalysis of Individual Patient Data from Randomised Adjuvant Trials

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| Chemo ± LHRH | n | RRR* | 95% CI | |
|---------------------|----------|-------------|------------------|----------|
| Age ≤ 40 years | 714 | -24.7 | (-39.5 to 6.2), | p = 0.01 |
| Age > 40 years | 1662 | - 5.1 | (-20.1 to 12.7), | p = 0.55 |

Chemo + Tam ± LHRH

| | | | | |
|----------------|-----|-------|------------------|----------|
| Age ≤ 40 years | 81 | -31.2 | (-67.5 to 46.0), | p = 0.33 |
| Age > 40 years | 284 | 5.3 | (-33.3 to 66.3), | p = 0.82 |

(Chemo ± Tam) ± LHRH (combination of previous comparisons: chemo ± LHRH and chemo + Tam ± LHRH!)

| | | | | |
|----------------|-----|-------|------------------|----------|
| Age ≤ 40 years | 795 | -25.2 | (-39.4 to -7.7), | p = 0.01 |
| Age > 40 years | 284 | - 3.9 | (-18.1 to 12.9), | p = 0.63 |

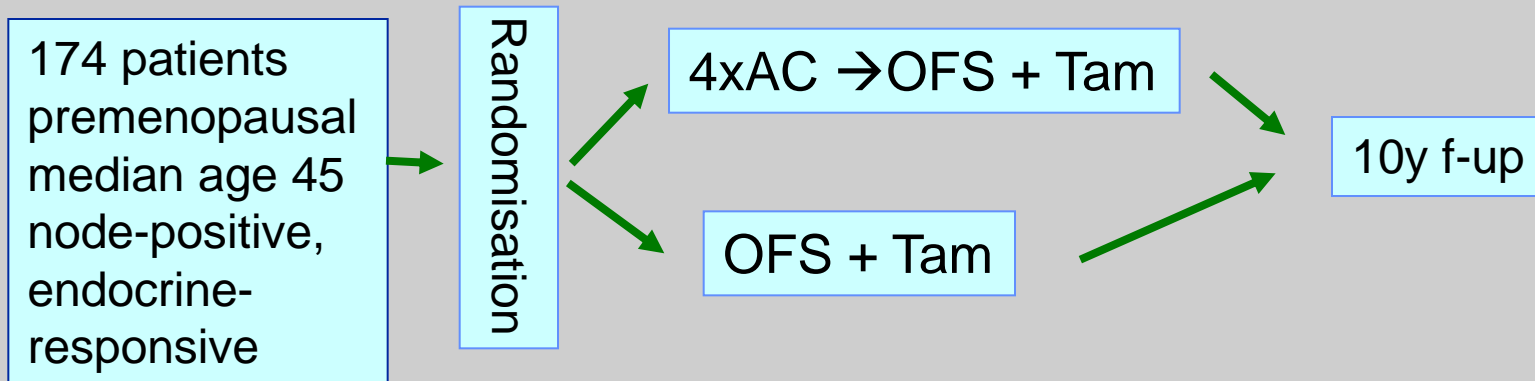
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* relative risk reduction

Cuzick J et al., Lancet 2007; 369:1711-23

Chemo + Castration + Tam vs. Castration + Tam



DFS hazard ratio = 1.02 (0.57-1.83); P = 0.94

OS hazard ratio = 0.97 (0.44-2.16); P = 0.94

- Trial was closed prematurely due to low accrual rate.
- No evidence that AC chemotherapy provides additional disease control for premenopausal patients with lower-risk node-positive endocrine-responsive breast cancer who receive adequate adjuvant endocrine therapy.

GnRH-a: RCTs

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| | Badawy (2009) | | Ismail-Khan (2008) | | ZOR0 (2009) | |
|--------------------------|--------------------------------|------------|--------------------|-------------|-------------------|---------------|
| | Chemo+ GnRH-a | Chemo | Chemo+ GnRH-a | Chemo | Chemo+ GnRH-a | Chemo |
| N | 39 | 39 | 25 | 24 | 30 | 30 |
| Pts.-character. | | | | | | |
| pT | - | - | - | - | 1–4 | 1–4 |
| N+ | - | - | 50 % | 50 % | 35% | 42% |
| Horm. rec. pos. | - | - | - | - | 0% | 0% |
| Age (med., years) | 30 | 29 | 39 | 39 | 35 | 38 |
| Med. F/U [mths] | 8 | 8 | 18 | 18 | 24 | 24 |
| GnRH-a appl. | during Chemo | | during Chemo | | during Chemo | |
| Chemotherapy | 6x FA ₅₀₀ C d1q6-8w | | 6x FAC, AC-T, TAC | | 6x FEC, AC-T, TAC | |
| Regular menstr. | | | | | | |
| ≤1 year | 90% | 33% | 83% | 79% | 83% | 80% |
| - end of F/U | - | - | 88% | 84% | 93% | 97% |
| Pregn. / Births | - | - | 0 | 8% | 3% / 3% | 3% / 0 |

GnRHa: Observation Studies

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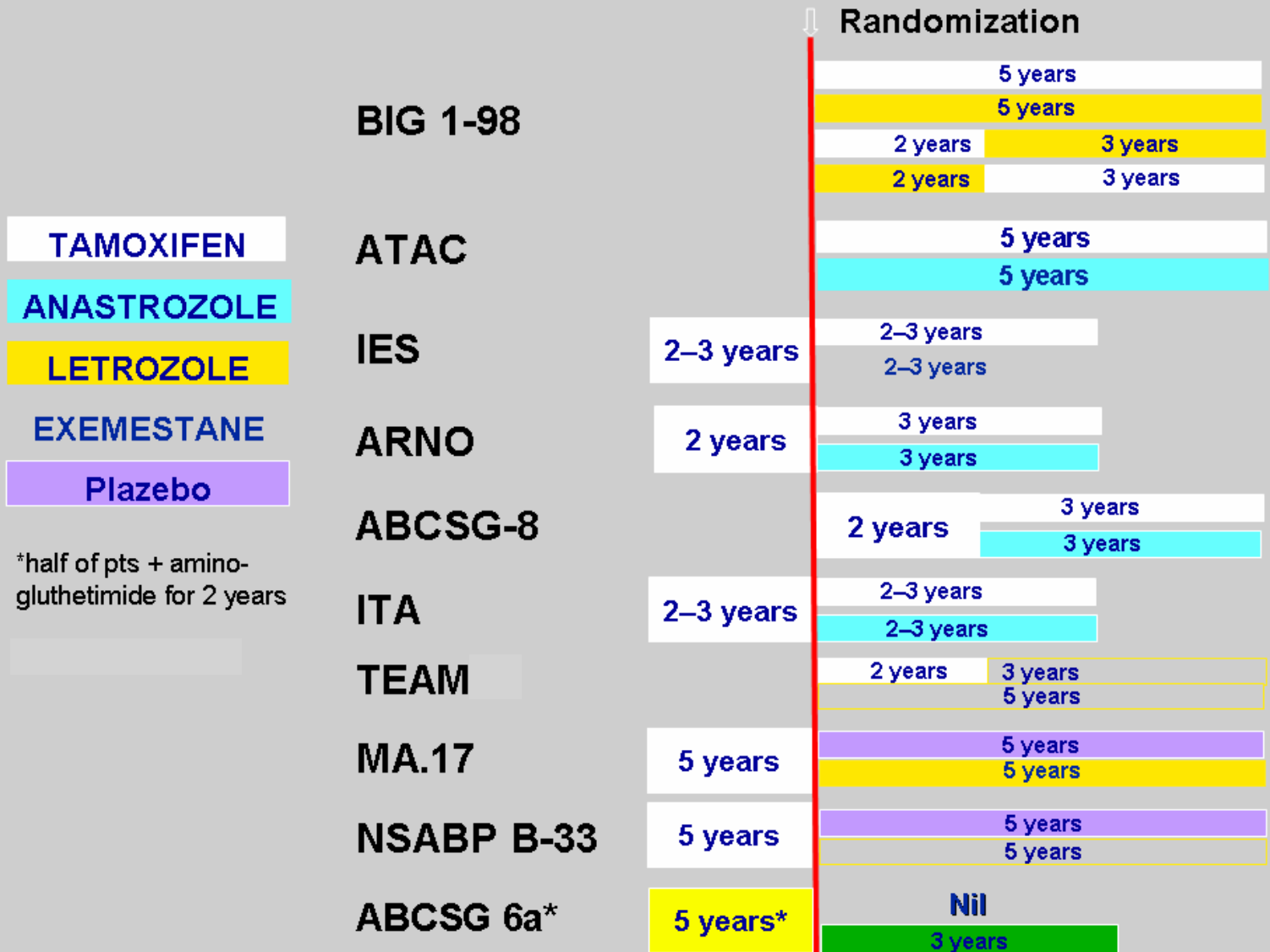
| | Recchia 2006 | Fox 2003 | Del Mastro 2006 | Urrutico- echea 2008 |
|--|--|---------------------------------------|--|-------------------------------------|
| N | 100 | 24 | 29 | 60 |
| Pts.-charact. | | | | |
| pT | 2–3 | 1–2 | 1–3 | - |
| N+ | 58% | 50% | 55% | - |
| Horm. rec. pos. | 52% | - | 86% | 72% |
| Age (med., years) | 43 | 35 | 38 | 34 |
| Med. F/U [mths] | 75 | 34 | 72 | 43 |
| GnRH-a application | during Chemo up to 1 year | during Chemo | | |
| Chemotherapy | FAC, CMF, E₁₂₀- CMF, Taxane, high-dose Chemo | AC, AC-T, FAC, AT- CMF | FEC, AC-T | FEC, FEC-T, AC, EC-T |
| Regular menstr. ≤1 year after Chemo | 100% (<40 y.) 56% (>40 y.) | 96% - | 94% (<40y) 42% (>40y) | 86% - |
| Pregnancies/ Births | 3% / 2% | 21% / 8% | - | 20% / 16% |

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Trials with Aromatase Inhibitors

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Aromatase Inhibitors in Adjuvant Therapy

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Overview over Published Trials: Upfront and Extended Therapy

| Trial | Source | AI | Indication | Pts | F/U mo | DFS/BCFS/TTR/TTDR/CBC | OS | Side Effects | Remarks |
|-----------------|-----------------------------------|----|----------------------------|------|--------|---|-----------------------|--|---|
| ATAC | ATAC Trialists' Group 2010 | A | upfront vs T | 6241 | 120 | HR + patients: DFS HR 0.86, p=0.003 TTR 0.79, p=0.0002 TTDR 0.85, p=0.02 | HR 0.87 p=0.4 | SAE T>A gyn AE T>A VE T>A SE A>T | only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL → (Cella 2006) |
| BIG 1-98 | BIG 1-98 Collaborative Group 2011 | L | upfront ² vs T | 4922 | 97 | DFS = 0.86 P = 0,007 | P = 0,048 | SAE T=L gyn AE T>L TE T>L CE L>T SE L>T | L>T in particular in case of N+ |
| NCIC CTG MA.27 | Goss 2010 | E | upfront vs A | 7576 | 49 | EFS HR 1.02 DDFS HR 0.95 | ns | Osteoporosis A>E El. liver enzymes E>A Hyperlipidaemia A>E | Randomization for Celecoxib cancelled |
| Extended | Adjuvant | | Therapy | | | | | | |
| MA 17 | Goss 2005 | L | extended after 5y T vs P | 5170 | 30 | DFS HR 0.58, p<0.01 TTDR HR 0.60, p<0.01 CBC HR 0.63, p=0.13 | HR 0,61 in N+, p=0,04 | CE L=P SE L>P | QoL ↓ (Whelan 2005) Lipids → (Wasan 2005) |
| ABSCG6a | Jakesz 2007 | A | extended after 5y T vs Nil | 856 | 62 | DFS HR 0.642 p=0.031 | ns | | |
| NSABP-B33 | Mamounas 2008 | E | Extended after 5y T Vs P | 1598 | 30 | DFS HR 0,68 p=0,07 RFS HR 0,44 p= 0,004 | ns | SE E=P after 6 Mo | Grad 3 AE E>P 9%vs3%, p=0,03 Profit from E particular in N+ |

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A anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; SAE, serious adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. * only HR positive population

Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Switching/Sequential trials

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| Trial | Source | AI | Indication | Pts | F/U mo | DFS/BCFS/TTR/ TTDR/CBC | OS | Side Effects | Remarks |
|---------------------------|----------------------|----|---|--------------|-----------|---|---|---|--|
| IES | Bliss JM | E | switch after 2-3y T vs T | 4599 | 91 | DFS HR 0.76, ITT p<0.01 DFS HR 0.75, ER+/u BCFS HR 0.76, ITT, s BCFS HR 0.75, ER+/u TTDR HR 0.83, ITT, s TTDR HR 0.82 ER+/u, s | HR, 0.86; 95% CI, 0.75 to 0.99; P = .04). | gyn AE T>A TE T>E SE E>T diarrhea E>T | Random after 2-3y T, only pts. relapse-free after 2-3 y T were included |
| ITA | Boccardo 2006 | A | switch after 2-3y T vs T | 448 | 64 | EFS HR 0.57, p<0.01 RFS HR 0.56, p=0.01 | ns | SAE T>A | Random after 2-3y T, only pts. relapse-free after 2-3 y T were included |
| ABCSG - 08 ARNO95 | Jakesz 2005 | A | switch after 2y T vs T | 3224 | 28 | DFS HR 0.59, p<0.01 TTR HR 0.60, p<0.01 TTDR HR 0.61, p<0.01 | ns | TE T>A SE A>T | |
| ABCSG -08 | Jakesz 2005 | A | switch after 2y T vs T | 2529 | 31 | DFS HR 0.61, p=0.01 TTDR HR 0.68, p=0.11 CBC HR 0.45, p=0.07 | ns | TE T>A SE A>T | Analysis of switch data only, random upfront |
| ARNO 95 | Kaufmann 2007 | A | switch after 2y T vs T | 979 | 30 | DFS HR 0.66, p=0.049 | HR 0.53, p=0.045 | SAE T>A 30,8 vs 22,7 % | No chemotherapy, random after 2 y T; only pts relapse-free after 2 y T were included |
| BIG 1-98 | Regan et al 2011 | L | switch after 2y T vs. Let switch after 2y L vs. Let. | 1548 1540 | 97 | disease-free survival; 87.5%, 87.7%, 85.9% ns | 89.9%, 88.7%, 88.1% ns | SE L>T VE L = T | Comparison of switch L/T or T/L vs. L |
| TEAM | Van de Velde 2011 | E | TEAM: E alone vs Tam switch after 2 – 3 y to E | 4868 4898 | 60 | hazard ratio 0.97, 95% CI 0.88-1.08; p=0.60) | n.a. | DVT; endometrial > switch Musculoskeleta l problems hyperlipidaemi a > E mono | |
| N-SAS BC03 | Aus Japan 2010 | A | Tam 5 y vs Tam→ A switch after 1 – 4 y Tam | 706 | 42 | DFS: 0.69 P = 0.14 RFS 0.54 P = 0.06 | n.a. | dito | |
| Meta- analysis | | | | | | | | | |
| ARNO95 ABSCG8 ITA | Jonat 2006 | A | switch (2-3y T) | 4006 | | DFS HR 0.59, p<0.01 | HR 0.71, p=0.04 | | with heterogeneity |

A, anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; Cx, chemotherapy; DFS, disease-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; ITT, intent to treat; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; s, significant; serious adverse event; SE, skeletal event; T tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; u, unknown; VE, vascular event; (?) according to retrospective analysis.

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Adjuvante zytostatische und zielgerichtete Therapien

Adjuvante zytostatische und zielgerichtete Therapie

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- **Version 2002:**
Möbus / Nitz
- **Versionen 2003–2013:**
**Harbeck / Jackisch / Janni / Loibl /
von Minckwitz / Möbus / Müller / Nitz
Schneeweiss / Simon / Solomeyer /
Stickeler / Thomssen**
- **Version 2014:**
Untch / von Minckwitz

Subtyp-spezifische Strategien zur Systemtherapie

AGO

- **HR+/HER2- mit „niedrigem Risiko“**
 - Endokrine Therapie ohne Chemotherapie **++**
- **HR+/HER2- mit „hohem Risiko“**
 - Konventionell dosierte AT-basierte Chemotherapie **++**
 - Dosisdichte, dosis-intensivierte Chemotherapie bei großer Tumorlast **+**
 - Anschließend endokrine Therapie **++**
- **HER2+**
 - Trastuzumab plus **++**
 - Sequenzielles A/T-basiertes Regime mit simultaner Gabe von T+H **++**
 - Anthrazyklin-freie, Platin-haltige Therapie **+**
 - Dosisdichte, dosis-intensivierte Chemotherapie bei großer Tumorlast **+**
- **Triple-negativ (TNBC)**
 - Konventionell dosierte AT-basierte Chemotherapie **++**
 - Dosisdichte, dosis-intensivierte Chemotherapie **+**

Wenn die Indikation für eine Chemotherapie gegeben ist, sollte zuerst eine neoadjuvante Verabreichung erwogen werden ++

Adjuvante Chemotherapie ohne Trastuzumab: Übersicht

Oxford / AGO
LoE / GR

- | | | | |
|--|-----------------------|----------|-----------|
| ➤ Anthrazykline (anstatt CMF) | 1a | A | ++ |
| ➤ Taxane | 1a | A | ++ |
| ➤ Dosisdichte Therapie (N+) | 1a | A | ++ |
| ➤ CMF (anstatt keiner Therapie) | 1a | A | ++ |
| ➤ EC - T (anstatt FEC – T) | 1b^a | A | ++ |

Anthrazyklin-freie Regime ohne Trastuzumab

Oxford / AGO
LoE / GR

Äquivalente Effektivität (OS) zu ≥ 4 x AC (EC):

- | | | | |
|-----------------|----|---|-----|
| ➤ 4-6 x Pac q3w | 1b | B | +/- |
| ➤ 6 x CMF | 1a | A | +/- |

Verbesserte Effektivität (OS) zu 4 x AC :

- | | | | |
|----------|----|---|---|
| ➤ 4 x DC | 1b | B | + |
|----------|----|---|---|

Taxane

Optimale Kombinationen und Dosierungen

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Regime

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| | | | | | |
|---|---------------------------|--|-----------------------|----------|-----------|
| ➤ | EC → P_w | E₉₀C q3w x 4 → P₈₀ qw1 x 12 | 1b^a | B | ++ |
| ➤ | DAC | D₇₅A₅₀C q3w x 6 | 1b | A | ++ |
| ➤ | AC → P_w | A₆₀C q3w x 4 → P₈₀ qw1 x 12 | 1b | A | ++ |
| ➤ | AC → D | A₆₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b | A | ++ |
| ➤ | EC → D | E₉₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b^a | B | ++ |

Empfohlene Taxan-haltige Regime

Standarddosierungen

Oxford / AGO
LoE / GR

Kombinationsregime

| | | | | |
|-------|--------------------------|----|---|-----|
| ➤ DAC | (BCIRG 001, anstatt FAC) | 1b | A | ++ |
| ➤ DC | (US Oncol., anstatt AC) | 1b | A | + |
| ➤ AD | (E2179, anstatt AC) | 2b | B | +/- |

Sequentielle Regime (gleiche Dauer)

| | | | | |
|--------------------------|------------------------------------|-----------------|---|----|
| ➤ EC→Pw | (GIM, anstatt FEC→Pw) | 1b ^a | B | ++ |
| ➤ FEC → D | (PACS 01, anstatt FEC) | 1b | B | + |
| ➤ AC → Pw | (E1199, anstatt AC → P3w) | 1b | A | ++ |
| ➤ FE ₆₀ C → D | (TACT, anstatt FE ₆₀ C) | | | |
| | (TACT, anstatt E → CMF) | 2b | B | - |
| ➤ AP → CMF | (ECTO, anstatt A → CMF) | 2b | B | + |

Sequentielle Regime (ungleiche Dauer)

| | | | | |
|--------------------------|--|-----------------|---|-----|
| ➤ AC → P | (NSABP B-28, anstatt AC) | 1b | A | + |
| ➤ FEC → P | (GEICAM 9906, anstatt FEC) | 2b | B | + |
| ➤ AC → D | (BCIRG 005, anstatt DAC) | 1b ^a | B | ++ |
| ➤ EC → D | (WSG/AGO, anstatt FE ₁₀₀ C) | 1b ^a | B | ++ |
| ➤ EC → D | (ADEBAR, anstatt FE ₁₂₀ C) | 1b ^a | B | +/- |
| ➤ A → D → CMF > AD → CMF | (BIG 2-98, anstatt A ± C → CMF) | 2b | B | + |
| ➤ E → D → CMF | (TAXIT 216, anstatt E → CMF) | 2b | B | +/- |

In Studien mit adäquat dosierten Anthrazyklinen erscheint der Benefit von Taxanen vergleichsweise gering. In der Sequenz AC-Taxane, gibt es aktuell keine Evidenz für einen Vorteil eines der beiden Taxane. Neben den substanzspezifischen Nebenwirkungen war die wöchentliche Gabe generell weniger toxisch. (LoE 2b^a, B)

Adjuvante Chemotherapie (weitere Medikamente)

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LoE / GR**

Capecitabine enthaltende Regime

(im Fall von HER2 neg., ER/PR neg., TPN)

1a B +/-

E-Cis-F

2b B +/-

Gemcitabine enthaltende Regime

-

Adjuvante Chemotherapie (dosisdicht und / oder dosiseskaliert)

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Dosis-dichte Regime (N +)

- dd ACP / AC-P q2w (anstatt q3w)
(CALGB 9741)
- AC / ddP q1w x 12 (anstatt P q3w)
- *EC / ddP q1w x 12 (anstatt P q3w)
- EC/ddP q2w (anstatt q3w)
- AC/ddP q1w (anstatt q2w)
- ddEC q2w/ ddP q1w (anstatt EC q3w)
- ddE₁₂₀C₈₃₀ q2w x 6 => P q3w x 4
- ddAC→Pq2w = 6x TAC

Oxford / AGO LoE / GR

| | | |
|-----------------|---|-----|
| 1b | A | + |
| 1b | A | ++ |
| 1b | B | ++ |
| 1b ^a | A | + |
| 1b ^a | A | ++ |
| 2b ^a | B | + |
| 1b | A | +/- |
| 1b | A | +/- |

Dosis-dichte und dosis-eskalierte Regime (N ≥ 4+)

- dd E-P-C q2w (anstatt EC-P q3w) (AGO)

| | | |
|----|---|----|
| 1b | A | ++ |
|----|---|----|

* Extrapolated from doxorubicin trials

Adjuvante Therapie mit Trastuzumab I

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LoE / GR**

- **Nodal-positive Erkrankung**
- **Nodal-negative Erkrankung
(wenn Chemotherapie als indiziert
angesehen wird)**
 - **10 mm**
 - **>5-10 mm**
 - **≤ 5 mm**

1a A ++

1a A ++

2b B +

2b B +/-

Adjuvante Therapie mit Trastuzumab II

Oxford / AGO
LoE / GR

Beginn der Therapie

- **Simultan mit Taxanen**
- **Bis zu 3 Monaten nach Chemotherapie**

| | | |
|-----------|----------|-----------|
| 1a | A | ++ |
| 1b | B | + |

Dauer der Therapie

- **Für 1 Jahr**
- **Für 2 Jahre**
- **Für ½ Jahr**

| | | |
|-----------------------|----------|-----------|
| 1b | A | ++ |
| 1b^a | B | - |
| 1b^a | B | - |

Dosierung der Therapie

- **2 (4*) mg/ kg wöchentlich**
- **6 (8*) mg/ kg alle drei Wochen**

| | | |
|-----------|----------|-----------|
| 2b | B | ++ |
| 2b | B | ++ |

* Loading dose

Trastuzumab Adjuvant

Überwachung hinsichtlich CHF

Oxford LoE: 5

GR: D

AGO: ++

Vor Beginn der Trastuzumab-Therapie

- Anamnese, klinische Untersuchung (Ödeme, Hepatomegalie)
- Echokardiographie (Alternative zu MUGA)

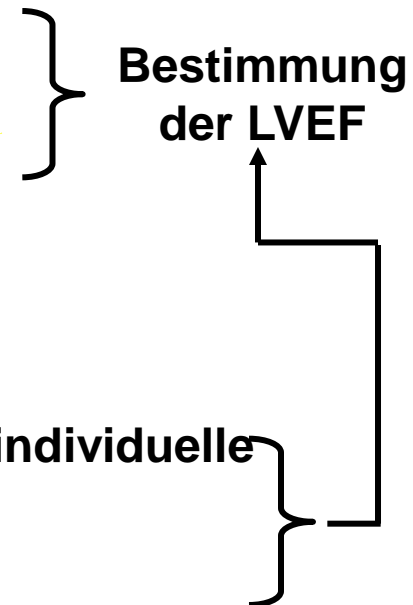
Bestimmung
der LVEF

Während und nach der Trastuzumab-Therapie

Regelmäßige Dokumentation von

- Herzfrequenz; bei Anstieg > 15 % über das individuelle Ausgangsniveau
- Körpergewicht; bei Anstieg ≥ 2 kg/Woche

LVEF alle 3 Monate



Adjuvante Therapie mit Trastuzumab: Regime

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Simultan mit

- **Paclitaxel / Docetaxel nach AC / EC**
- **P q1w 12 x ohne A bei pT (< 3 cm), pN0**
- **Docetaxel und Carboplatin**

- **Mit Anthrazyklinen**
- **Mit Taxan dosis-dicht**

**Oxford / AGO
LoE / GR**

1b A ++

2b^a B +/-

1b A +

2b B +/-

2b B + *

Radiotherapie simultan zu Trastuzumab

2b B +

*** Studienteilnahme empfohlen**

Adjuvante Therapie mit anderen zielgerichteten Substanzen

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- | | | | |
|--|-----------------------|----------|-----------|
| ➤ Lapatinib | 5 | D | - |
| ➤ (verzögerte adjuvante Therapie) | 1b | B | - |
| ➤ Pertuzumab | 5 | D | - |
| ➤ Bevacizumab | 1b^a | B | -- |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Neoadjuvante (Primäre) systemische Therapie

Neoadjuvante systemische Therapie

- **Version 2002:**
Costa
- **Versionen 2003–2013:**
**Blohmer / Dall / Fersis / Göhring /
Harbeck / Heinrich / Huober / Jackisch /
Kaufmann / Lux / von Minckwitz / Müller /
Nitz / Schneeweiss / Schütz / Solomayer /
Untch**
- **Version 2014:**
Bauerfeind / Loibl

Allgemeine Überlegungen zur Systemtherapie in Abhängigkeit von Subtyp

AGO

- **HR+/HER2- und “niedriges Risiko”:**
 - Endokrine Therapie ohne Chemotherapie **++**
- **HR+/HER2- und “hohes Risiko”**
 - Konventionell dosierte AT-basierte Chemotherapie **++**
 - Dosisdicht und dosiseskaliert in Fällen mit hoher Tumorlast **+**
 - Sequentielle endokrine Therapie **++**
- **HER2+**
 - Trastuzumab plus
 - Sequentiell AT-basierte Protokolle mit T + H **++**
 - Anthrazyklin-frei, mit Carboplatin **+**
 - Dosisdicht und dosiseskaliert in Fällen mit hoher Tumorlast **+**
- **TNBC**
 - Konventionell dosierte AT-basierte Chemotherapie **++**
 - Dosisdicht und dosiseskaliert **+**
- Bei bestehender Indikation zur Chemotherapie sollte unbedingt die Möglichkeit der neoadjuvanten Chemotherapie erwogen werden. **++**

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

- **Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie**
- **Pathologische Komplettremission ist mit einem besseren Überleben assoziiert, besonders in Subgruppen**
- **Kann Operabilität bei primär inoperablen Tumoren erreichen**
- **Verbessert die Optionen für eine brusterhaltende Operation**
- **Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen**

**Oxford / AGO
LoE / GR**

| | | |
|----|---|----|
| 1a | A | |
| 1b | A | |
| 1b | A | ++ |
| 1b | A | ++ |
| 1b | B | +* |

*** Studienteilnahme empfohlen**

Neoadjuvante systemische Chemotherapie Indikationen

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|-----------|
| ➤ Inflammatorisches Mammakarzinom | 2b | B | ++ |
| ➤ Inoperables Mammakarzinom | 1c | A | ++ |
| ➤ Große operable Mammakarzinome, die primär eine Mastektomie und adjuvante Chemotherapie erfordern, mit dem Ziel der Brusterhaltung | 1b | B | + |
| ➤ Wenn die gleiche postoperative adjuvante Chemotherapie indiziert ist | 1b | A | + |
| ➤ Triple negatives Mammakarzinom (TNBC) | | | + |
| ➤ HER2 positives Mammakarzinom | 1b | B | + |

Neoadjuvante systemische Chemotherapie

Prädiktion des Ansprechens I

| Faktor | CTS | LoE _{Ox2001} | GR | AGO |
|----------------------------------|-----|-----------------------|----|-----|
| ➤ Jüngeres Alter | B | 1a | A | + |
| ➤ Kleinere Tumoren | B | 1a | A | ++ |
| ➤ Negativer Hormonrezeptorstatus | B | 1a | A | ++ |
| ➤ Triple negatives Mammakarzinom | B | 1a | A | ++ |
| ➤ Positiver HER2 Status | B | 1a | A | ++ |
| ➤ Nicht-lobuläre Histologie | B | 1a | A | + |
| ➤ Frühes klinisches Ansprechen | B | 1b | A | + |

Neoadjuvante systemische Chemotherapie

Prädiktion des Ansprechens II

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| Faktor | LoE ₂₀₀₉ | CTS | GR | AGO |
|------------------------------------|---------------------|-----|----|-----|
| ➤ PAM50/Mammaprint | III | C | B | +/- |
| ➤ Ki-67 | I | B | A | + |
| ➤ Tumor infiltrierende Lymphozyten | II | B | B | + |
| ➤ <i>PIK3CA</i> Mutation | II | B | B | + |

Neoadjuvante systemische Chemotherapie

Empfohlene Regime und Schedules

Oxford / AGO LoE / GR

- **Adjuvante Standardregime mit einer Dauer von mindestens 18 Wochen**

1a A ++

- **AC oder EC → D q3w oder P q1w**

2b A ++

- **DAC**

2b B ++

- **AP → CMF**

1b A +

- **Taxan gefolgt von Anthrazyklin**

2b B +

- **Dosisdichte Protokolle (z. B. E -P-CMF, E-P-C)**

1b B +*

- **Capecitabin in Kombination mit Anthrazyklin und Taxan**

1b B +/-

- **Platinsalze beim TNBC unabhängig von einer BRCA1-Mutation**

2b B +*

* Studienteilnahme empfohlen

Mögliche carboplatinhaltige Regime in der neoadjuvanten Situation

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| Autor | Studie | Regime | pCR Rate ypT0/is, ypN0 |
|-------------------------------------|-----------------------------|--|------------------------------|
| Positive Studien | | | |
| Sikov et al. (SABCS 2013) | CALGB 40603 Phase III | Paclitaxel 80mg/m ² weekly x 12+Carboplatin AUC 6q3w x4 – dd AC (q2w) | 49% 60% (+Bev) |
| von Minckwitz et al. (ASCO 2013) | Phase II | NPLD20mg/m ² + Paclitaxel 80mg/m ² +Carboplatin AUC 1.5mg/m ² weekly x18 | 53% (+Bev) |
| Negative Studien | | | |
| Alba et al. BCRT 2013 | Phase II basal like | EC (90/600mg/m ²)q3w x4 – Docetaxel 75mg/m ² + Carboplatin AUC 6 q3w x 4 | 30% |

Neoadjuvante systemische Chemotherapie

Empfohlene Methoden zum Messen des Ansprechens

Oxford / AGO LoE / GR

| | | | |
|---|-----------|----------|------------|
| ➤ Mammasonographie | 2b | B | ++ |
| ➤ Palpation | 2b | B | ++ |
| ➤ Mammographie | 2b | B | ++ |
| ➤ MRT | 2b | B | + |
| ➤ PET(-CT) | 1b | D | +/- |
| ➤ Clipmarkierung der Tumorregion | 5 | D | ++ |

Neoadjuvante zielgerichtete Therapie bei HER2-positiven Tumoren

**Oxford / AGO
LoE / GR**

- | | |
|--|-----------------------|
| ➤ Trastuzumab in Kombination mit Chemotherapie | 1b A ++ |
| ➤ Lapatinib in Kombination mit Chemotherapie | 1b B - |
| ➤ Lapatinib + Trastuzumab in Kombination mit Chemotherapie | 2b B +/- |
| ➤ Pertuzumab + Trastuzumab in Kombination mit Chemotherapie | 2b B +* |
| ➤ Zwei gegen HER2 gerichtete Substanzen ohne Chemotherapie | 2b B +/- |

*** Studienteilnahme empfohlen**

Neoadjuvante zielgerichtete Therapie bei HER2-negativen Tumoren

**Oxford / AGO
LoE / GR**

Chemotherapie in Kombination mit Bevacizumab

- **Beim Hormonrezeptor-positiven
Mammakarzinom**
- **Beim TNBC**

2b B +/-

1b C +/-

Neoadjuvante systemische Therapie Vorgehen bei einem frühen Ansprechen

Oxford / AGO
LoE / GR

**Bei frühem Ansprechen nach 6 bis 12 Wochen
einer neoadjuvanten Chemotherapie:**

- **Komplettierung der gesamten
Chemotherapie vor der Operation
d.h. ≥ 18 Wochen Behandlung** **1b A ++**
- **Beim Ansprechen nach 2 Zyklen TAC
beim HR-positiven Mammakarzinom
8 statt 6 Zyklen TAC erwägen** **2b C +**

Neoadjuvante systemische Therapie

Vorgehen bei keinem frühen Ansprechen

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Bei keiner Änderung:

- **Komplettierung der NST, anschl. Operation**
- **Fortsetzen der NST mit einem nicht-kreuzresistentem Regime**
 - **AC oder EC x 4 → D x 4 oder Pw x 12**
 - **DAC x 2 → NX x 4**

**Oxford / AGO
LoE / GR**

2b C ++

2b B +

2b B +

1b B +

Bei Progression:

- **Abbruch der NST und umgehende Operation oder Bestrahlung**
- **Zusätzliche adjuvante Chemotherapie mit nicht-kreuzresistenten Regimen**

4 D ++*

4 D +/-*

***Studienteilnahme empfohlen**

Neoadjuvante systemische Therapie

Lokoregionäre Operationen

**Oxford / AGO
LoE / GR**

- **Intraoperative Clipmarkierung
der Tumorregion** **5 D ++**
- **Adäquate Operation nach NST** **2b C ++**
- **Mikroskopisch freie Absetzungsrän-
der** **5 D ++**
- **Exzision innerhalb neuer Grenzen** **3b C +**
- **Sentinel node biopsy
(siehe Kapitel “Operation”)**

Operative Therapie der Axilla vor und nach NACT

Oxford / AGO
LoE / GR

SLNB vor oder nach NACT bei cN0

| | | | |
|----------------|----|---|-----|
| SLNB vor NACT | 2b | B | + |
| SLNB nach NACT | 3 | B | +/- |

Weitere operative Therapie in Abhängigkeit von SLNB

| cN-Status (vor Therapie) | pN-Status (vor Therapie) | cN-Status (nach Therapie) | operatives Vorgehen | | | |
|-----------------------------|---------------------------------|------------------------------|------------------------|---------|--------|----------|
| cN0 | pN0(sn) | - | nihil | 1a | A | + |
| cN0 | pN+(sn) analog ACZOZOG | ycN0 | ALND | 3 | B | +/- |
| cN0 | pN+(sn) nicht analog ACZOZOG | ycN0 | ALND | 2b | B | + |
| cN+ | cN+ (CNB/FNA) | ycN0 | SNB ALND | 3 2b | B B | +/- + |
| | | ycN+ (CNB/FNA) | ALND | 2b | B | ++ |

Neoadjuvante systemische Therapie

Indikationen für Mastektomie

**Oxford / AGO
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- **Positive Absetzungsränder trotz mehrfacher Nachresektion** 3b C ++
- **Radiotherapie nicht durchführbar** 5 D ++
- **Bei einer klinisch kompletten Remission**
 - **Inflammatorisches Mammakarzinom** 2b C +
 - **Bei pCR** +/-
 - **Multizentrisches Mammakarzinom** 3 C +/-
 - **cT4a-c Mammakarzinom** 2b B +/-

Neoadjuvante systemische Therapie

Zeitablauf von Operation und Radiotherapie

Oxford / AGO
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Operation

4 C ++

- Nach Leukozyten-Nadir
(2 bis 4 Wochen nach dem letzten
Chemotherapiezyklus)

Radiotherapie nach Operation

2b B ++

- 2–3 Wochen nach Operation
- Indikation gemäß Krankheitsstadium
vor NST (cN+, cT3/4a-d)

Adjuvante systemische Therapie nach neoadjuvanter systemischer Therapie

Oxford / AGO
LoE / GR

- Endokrine Therapie bei
endokrin-sensitiver Erkrankung
- Komplettierung der Trastuzumab-
Behandlung auf bis zu 1 Jahr bei
HER2-positiver Erkrankung
- Bei ungenügendem Ansprechen
 - Weitere Chemotherapie
 - Experimentelle Behandlung

1a A ++

2b B ++

3 C -

5 D +

Neoadjuvante endokrine Therapie

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| | 2a | B | + |
| ➤ Postmenopausale Patienten mit endokrin sensiblen Mammakarzinom, die inoperabel sind und keine Chemotherapie möchten / haben können | | | |
| ➤ Verbessert die Optionen für brusterhaltende Operationen bei postmenopausalen Frauen mit endokrin sensiblen Mammakarzinom | 1b | A | + |
| ➤ Aromataseinhibitoren (für > 3 Monate) | 1b | B | + |
| ➤ Prämenopausale Patientinnen mit endokrin sensiblen Mammakarzinom, die inoperabel sind und keine Chemotherapie möchten / haben können | | | + |
| ➤ Tamoxifen | 2b | C | + |
| ➤ Aromatase inhibitors+LHRH | 1b | C | +/- |
| ➤ Simultane chemo-endokrine Therapie | 1b | A | - |
| ➤ Prognostische Faktoren während/nach NST: Quantitative ER-Expression, Expression von Ki-67, N-Status, T-Status (PEPI) | 1b | B | + |

Optimale Dauer der neoadjuvanten endokrinen Therapie ist unbekannt.

Keine Langzeitergebnisse zur neoadjuvanten endokrinen Therapie (vs. adjuvante endokrine Therapie).

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Adjuvante Strahlentherapie



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Adjuvante Radiotherapie (RT)

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- **Versionen 2002 – 2013:**
**Souchon / Blohmer / Friedrichs / Göhring /
Janni / Möbus / Seegenschmiedt**

- **Version 2014:**
Souchon / Blohmer

Vorbemerkung

- **In wenigen Stellungnahmen weichen die aufgrund der vorhandenen Evidenz erarbeiteten Empfehlungen der AGO von denjenigen der Fachgesellschaften der Radioonkologen (DEGRO und ARO) ab. Dies ist auf den Folien jeweils kenntlich gemacht.**
- **Gegenwärtig wird mit diesen Fachgesellschaften eine gemeinsame Empfehlung für das klinische Vorgehen erarbeitet.**

Postmastektomie-Radiotherapie (PMRT)* der Thoraxwand

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- **>3 positive Lymphknoten**
 - **1-3 positive Lymphknoten (abhängig vom Alter der Patientin)**
 - **T3 / T4**
 - **pT3 pN0 R0 (und keine zusätzl. Risikofaktoren)**
 - **R0-Resektionsstatus nicht erreichbar (invasives Ca.)**
 - **Nach primärer systemischer Therapie (NACT):**
Indikation basiert auf prätherapeutischem Stadium:
Initiales Stadium vor PST (NACT): cN+, cT3/4a-d
 - **Bei jungen Pat. mit hohem Rückfallrisiko**
 - **Verzicht auf RT bei ypT0 ypN0 nach PST (NACT)°**
 - **Mit RT der supra-/infraklav. Lymphwege bei >3 ax. +Lnn.**
 - **Mit RT weiterer regionaler Lymphabflusswege (IM-LK)**
bei hohem Risiko / pN0 oder pN1-3
- *Indikationen zur PMRT und regionalen RT bestehen unabhängig von der Durchführung einer adjuvanten systemischen Therapie**

Oxford / AGO LoE / GR

| | | |
|----|---|-----|
| 1a | A | ++ |
| 1a | A | + |
| 1a | A | ++ |
| 2b | B | +/- |
| 1a | A | + |
| 2a | A | + |
| 2b | C | ++ |
| 3b | C | +/- |
| 1a | A | ++ |
| 2a | B | +/- |
| 1a | A | ++ |

RT nach brusterhaltender Operation (BEO) beim invasiven Karzinom

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- **Homogene perkutane RT der verbliebenen Brust (WBI)**
 - Normo-/standardfraktionierte WBI
 - Hypofraktionierte WBI +/- sequentieller Boost)
- **Boost-Radiotherapie (verstärkt die lokale Tumorkontrolle)**
 - Dosis-Wirkungsbeziehung unabhängig vom Patientenalter
 - Absoluter Benefit abhängig vom Alter der Patientin
- **Boost-RT bei nodal negativen, endokrin beeinflussbaren, komplett resezierten Tumoren**
- **Intraoperative Radiotherapie (IORT/IOERT)**
 - Als Boost-RT vor WBI
 - Als alleinige Radiotherapie
 - IORT mit 50 kV (pT1, N0, G1-2, kein lobular-invasives Karzinom, R0, Alter>50 J, kein extensives DCIS, IORT während der ersten Operation, HR+)
 - IOERT
- **Brachytherapie als alleinige Radiotherapie**
 - Interstitielle Brachytherapie
 - Intrakavitäre Ballon-Technik

Oxford / AGO
LoE / GR

| | | |
|----|---|------|
| 1a | A | ++ |
| 1a | A | +° |
| 1a | A | ++° |
| 1a | A | + |
| 1b | | |
| 1b | | |
| 3a | C | +/- |
| 2a | B | + |
| 1b | B | +* |
| 1b | B | -* |
| 1b | B | +/-* |
| 1b | C | -* |

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° Empfehlungsgrad (GR) abweichend von dem der aktuellen DEGRO Leitlinie 2013/14 *Studienteilnahme empfohlen

Boost-RT nach BEO beim invasiven Karzinom

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|-------------|
| ➤ Verbesserte lokale Tumorkontrolle | 1b | A | + |
| ➤ Alle Altersgruppen: LRR Reduktion (7-12%) | 1b | A | + |
| ➤ <40-jährige: LRR Reduktion (10-29%) | 1b | A | ++ |
| ➤ High grade invasives duktales Karzinom | 2b | A | + |
| ➤ Zusätzliche Boost-RT ohne Einfluss auf Überlebenswahrscheinlichkeit (10-Jahres-Daten) | | | |
| ➤ Keine verstärkten Nebenwirkungen bei hypofraktionierter WBI, wenn Boost nach WBI erfolgt | | | |
| ➤ Hypofraktionierte WBI + sequentieller Boost | 1b | B | + |
| ➤ Hypofraktionierte WBI + simultaner integrierter Boost | 2b | C | +/-* |
| ➤ Normofraktionierte WBI + simultaner integrierter Boost | 1b | B | + |
| ➤ Intraoperativer Boost + hypofraktionierte WBI | 5 | D | -* |

*Studienteilnahme empfohlen

Radiotherapie der Axilla

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| ➤ Tumorresiduen nach axillärer Dissektion | 2b | B | ++ |
| ➤ Sentinel-Lymphknoten negativ | 1 | B | -- |
| ➤ Axilladissektion nicht indiziert (z.B. bei positivem SLN; siehe Kapitel op. Therapie) | 2a | B | - |
| ➤ Extrakapsuläre Tumoraussaat (ECS) | 2b | B | -- |
| ➤ Axilläre Mikrometastasen oder isolierte Tumorzellen in regionalen Lymphknoten | 3b | B | -- |
| ➤ Anstelle einer indizierten axillären Lymphonodektomie bei positivem SLN ^o | 1 | B | +/- |

^o AMAROS trial

Radiotherapie der übrigen lokoregionalen Lymphabflussregionen

Oxford / AGO LoE / GR

➤ RT der supra-/infraklavikulären Lymphregion:

- Level III befallen
- Sofern RT der Axilla erfolgt
- pN1a
- pN2a
- (p)N3a-c
- Nach NACT (wenn prätherap. LK-Status positiv)*

| | | |
|----|---|-----|
| 1 | B | + |
| 3b | B | + |
| 1 | A | +/- |
| 1 | A | ++ |
| 1 | A | ++ |
| 3 | C | +/- |

➤ RT der Axilla:

- Nach Axillaclearing der Level I + II
- SNB -
- Bei Kontraindikation oder Ablehnung eines
suffizienten Axillaclearing

| | | |
|-----------------|---|-----|
| 3b | D | - |
| 4 | D | - |
| 2a ^a | B | +/- |

➤ RT der Mammaria-interna-Lymphabflussregion

| | | |
|---|---|-----|
| 1 | B | +/- |
|---|---|-----|

Der jeweilige Anteil der RNI pro erfasster RT-Region (SCN vs. IMN) am verbesserten Outcome kann nicht differenziert werden

**beachte Risiko-Nutzen-Relation der RT

^aAMAROS trial

Radiotherapie der übrigen lokoregionalen Lymphabflussregionen

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- RT der Mammaria-interna-Lymphabflussregion*: **1 B +/-**
- N2b, N3b
- \geq pN1b (Befall der Mammaria-interna-LK,
festgestellt durch SNB)
- pN1c – pN3c **1 B +/-**
- medialer/zentraler Tumorsitz,
pN0 +/- Risikofaktoren **1 B +/-**

* RT des Mammaria-interna-Lymphabflusses kann Vorteile ergeben bzgl. Überleben (OS), Metastasen-freiem Überleben (DMFS) und lokoregionaler Tumorkontrolle (LRR) entsprechend aktuell publizierter RCT und einer Metaanalyse

Kombination systemischer Therapien mit simultaner Radiotherapie

Oxford / AGO
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- **Trastuzumab simultan zur
Radiotherapie**
- **Tamoxifen simultan zur
Radiotherapie**
- **AI (Letrozol) simultan zur
Radiotherapie**

2b B +

3b C +

2a B +/-

Radiatio im Alter nach BEO

Oxford / AGO
LoE / GR

- **Verzicht auf Radiotherapie in low risk,
wenn endokrine Therapie durchgeführt wird***

1b A +

**Lokalrezidiv erhöht, kein Einfluss auf OS, Verminderung der
Toxizität**

*** ≥ 70 Jahre, pT1 , pN0, rez. pos, G1-2, HER2neu negativ,
Resektionsrand >1 mm**



Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Nebenwirkungen der Therapie

Nebenwirkungen der Therapie

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Friedrichs / Gerber / Göhring / Jackisch /
Lisboa / Müller / Nitz / Schmidt / Souchon
/ Stickeler / Untch**

- **Version 2014:**
Huober / Brunnert

Toxizitäts-Beurteilung

Akute Toxizität nach WHO¹ oder NCI-CTC²

Grad

0 keine
1 mild
2 mäßig
3 ausgeprägt
4 lebensbedrohlich

Notwendige Informationen

Beteiligte Organe
Art der Toxizität
Zeitintervall nach Behandlung
Effekt auf den Allgemeinstatus
Behandlungsnotwendigkeit
Erreichen einer Verbesserung

Langzeittoxizität

Keine allgemeines kategorisiertes Bewertungssystem

¹ WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)

² NCI, NHI, Bethesda, USA, Common Toxicity Criteria, CTCAE v4.0 , (2010) <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

Chemotherapie – Akute Toxizitäten I

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| | Hämatologi- sche Toxizität | Übelkeit/ Erbrechen | Haar- verlust | Stomatitis | Kardio- toxizität | Nieren- toxizität | Leber- toxizität |
|-------------------------------------|----------------------------------|------------------------|------------------|------------|----------------------|----------------------|---------------------|
| Cyclophosphamide | ++ | ++ | + | + | + | ++ | |
| Methotrexate | ++ | + | + | ++ | + | ++ | + |
| 5-Fluorouracil | ++ | ++ | | ++ | + | | |
| Carboplatin | ++ | ++ | + | | | ++ | |
| Cisplatin | + | +++ | | | | +++ | |
| Capecitabine | + | + | | + | | | |
| Gemcitabine | ++ | + | | + | | | + |
| Epi-/Doxorubicin | ++ | ++ | +++ | ++ | + | | |
| Pegliposomal Doxorubicin | + | + | + | +++ | (+) | | |
| Liposomal Doxorubicin | + | + | + | ++ | (+) | | |
| Mitoxantrone | ++ | ++ | + | + | + | | |
| Paclitaxel | ++ | + | +++ | + | | | + |
| nab-Paclitaxel | + | + | +++ | | | | + |
| Docetaxel | ++ | + | +++ | ++ | | | |
| Vinorelbine | ++ | | (+) | + | | | |
| Eribulin | ++ | + | + | | | | |

Chemotherapie – Akute Toxizitäten II

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| | Allergie | | Blasen- toxizität | Neuro- toxizität | Kutane Toxizität | Diarrhoe |
|---------------------------|----------|---|----------------------|---------------------|---------------------|-------------------------------------|
| Cyclophosphamide | + | + | + | + | | |
| Methotrexate | + | | + | ++ | | |
| 5-Fluorouracil | | | | + | + | + |
| Carboplatin | | | | | | |
| Cisplatin | | | +++ | | | |
| Capecitabine | | | | | ++ | ++ |
| Gemcitabine | | | | | | Flue-like Synd., Ödeme |
| Epi-/Doxorubicin | + | | | | | Paravasate, Dextrazone |
| Liposomal Doxo. | + | | | + | | |
| Pegliposomal Doxo. | + | | | +++ | | |
| Mitoxantrone | | | | ++ | | |
| Paclitaxel | +++ | | ++ | | + | Myalgia |
| nab-Paclitaxel | + | | ++ | | + | Myalgia |
| Docetaxel | ++ | | + | ++ | + | Myalgia, Fluid retention, nails! |
| Vinorelbine | | | ++ | | | Thrombophlebitis, Obstipation |
| Eribulin | | | | ++ | | |

Langzeittoxizität Kardiotoxizität

Oxford / AGO
LOE / GR

- Äquivalente Kardiotoxizität von Doxorubicin und Epirubicin in den empfohlenen Dosierungen (450-500 bzw. 900-1000 mg/m² kumul. Dosis) 2b B
- Liposomale Anthrazykline (Doxorubicin) induzieren weniger Kardiotoxizität 1b B
- Risikofaktoren für Anthrazyklin- oder Trastuzumab-assoziierte Kardiotoxizität: 2b B
 - Alter
 - Übergewicht
 - Hypertonus
 - Hypercholesterinämie
 - Vorbestehende Herzerkrankungen (inkl. grenzwertige LVEF)
 - Diabetes mellitus
- Überwachung der Herzfunktion: Echokardiographie (LVEF oder SF in %) 3b C +

Toxizitätssteigerungen durch Behandlungskombinationen

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Kardiale Toxizität

| | | | |
|--|----|---|-----|
| ➤ Trastuzumab simultan zur Radiotherapie | 2b | B | + |
| ➤ Trastuzumab simultan zu Epirubicin | 2b | B | +/- |
| ➤ Trastuzumab simultan zu Doxorubicin | 2b | B | - |
| ➤ Anthrazykline simultan zur Radiotherapie | 2c | C | - |

Risiko Lungen- / Brustparenchymfibrosen

| | | | |
|---|----|---|-----|
| ➤ Tamoxifen simultan zu Radiotherapie | 3 | C | +/- |
| ➤ Chemotherapie simultan zu Radiotherapie | 1b | B | - |

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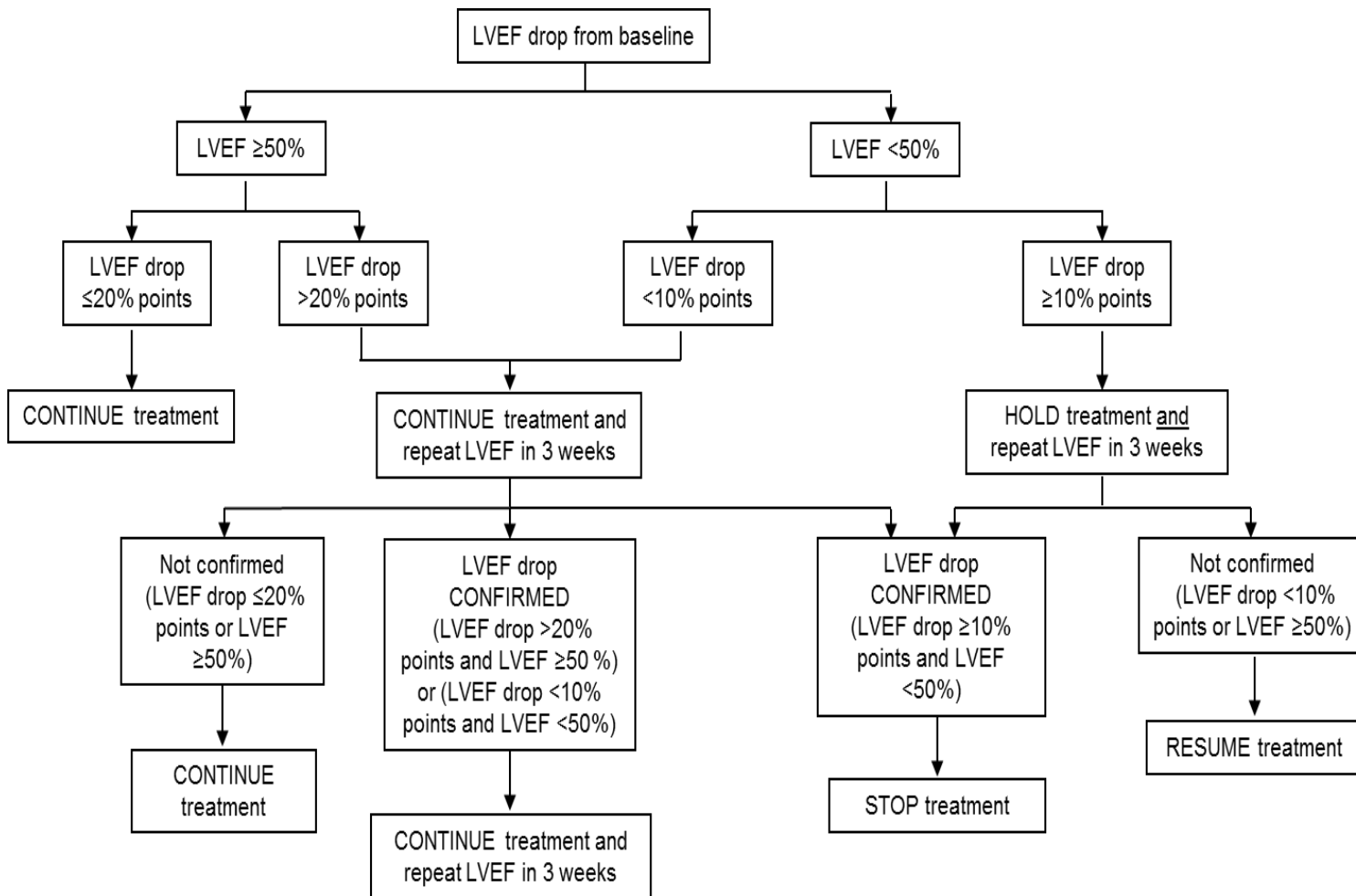
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Nebenwirkungen Trastuzumab/Pertuzumab

Algorithmus bzgl. kardialer Toxizität

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Sekundäre Malignome I

Oxford LoE / GR

- Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten
- Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2 – 0,4 % innerhalb von 10 - 15 Jahren
- Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2 – 1,7 % innerhalb von 8 - 10 Jahren
- Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2 – 0,4 %
- Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms

2a

2a

2a

2b

2b

Sekundäre Malignome II (nach Radiotherapie)

Oxford
LoE

- **Das Risiko für sekundäre Malignome ist bei Einsatz moderner Radiotherapie-Techniken niedrig und sollte diese, wenn indiziert, nicht verhindern**
- **Eine Postmastektomie-Radiotherapie (PMRT) kann das Risiko für ein ipsilaterales Lungenkarzinom und Angiosarkom mäßiggradig anheben (Auftreten 5 - 10 Jahre nach PMRT)**
 - **Erhöhtes Risiko besonders für Raucher**

2b

1a

2b

Chemotherapie assoziierte Amenorrhoe (CRA)

**Oxford
LoE**

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- **CRA kann dauerhaft oder vorübergehend sein**
- **Abhängigkeit vom Chemotherapie-Regime**
- **CRA ist ein (unsicherer) Surrogatmarker für Menopause und Fertilität**
- **Adjuvante endokrine Therapie induziert reversible Amenorrhoe, verschiebt aber Konzeption in eine weniger fertile Phase**
- **Das Risiko der CRA steigt mit dem Alter / Therapiedauer** **2b**
- **Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert** **2b**
- **CRA ist mit verbessertem Outcome (DFS/OS) verbunden** **1b**

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Synonyma: Chemotherapie / Therapie-induzierte Amenorrhoe (TIA/CIA)

(Therapie assoziierte) Fatigue

Oxford / AGO
LoE / GR

- **Fatigue häufiges Symptom bei Brustkrebspatientinnen (30-60%)** **2a B**
- **Ausschluss anderer Ursachen (Anämie, Tumorausdehnung, Begleiterkrankungen, Medikamente) für Fatigue** **1a A ++**
- **Gezielte psychosoziale Interventionen können Fatigue lindern** **1a A ++**
- **Körperliches Training kann Fatigue verbessern** **1b D +**
- **Methylphenidate kann Fatigue verbessern** **1a D +**

(Therapie assoziierte) Schlafstörungen

Oxford / AGO
LoE / GR

- **Schlafstörungen häufig bei Mammakarzinompatientinnen während und nach Therapie beschrieben (20-70%)**

2a B

- **Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität**

1b A ++

(Therapie assoziierte) Depressionen

Oxford / AGO
LoE / GR

- **Depressive Episoden bei 20-30% der Mammakarzinompatientinnen** **2a B**
- **Psychosoziale Interventionen verbessern Depressionen, allerdings ohne günstige Auswirkungen auf Mortalität** **1b A**
- **Antidepressiva können Depressionen bei Brustkrebspatientinnen verbessern** **1b A**
- **Körperliches Training kann Depressionen bei Brustkrebspatientinnen verhindern** **2b B +**

(Therapie assoziierte) Kognitive Störungen

Oxford / AGO
LoE / GR

- **Therapiebedingte kognitive Störungen
(sog. Chemobrain) häufig beschrieben
(16-75%)**
- **Verhaltenstherapie kann kognitive Funktion
verbessern**
- **Methyphenidate kann kognitive Funktion bei
Patientinnen mit Krebs verbessern**

2a B

2b B

3a C

Nebenwirkungen und Toxizitäten endokriner Substanzen I

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| | Sehstörungen | Osteoporose | Zerebro- vaskuläre Ereignisse * | Fraktur | Kardiale Risiko | Kognitive Funktion |
|--------------------|--------------|-------------|---------------------------------------|---------|--------------------|-----------------------|
| SERMs | (+) | | + | | | |
| AI 3rd Gen* | | + | | + | + | + |
| SERD | | + | | + | | |
| GnRH-a | | + | | + | | |

| | Arthralgie Myalgie | Hitze- wallungen | Blutungs- störungen * | Endo- metrium | Thrombose | Fettstoff- wechsel- veränd. |
|------------------|-----------------------|---------------------|-----------------------------|------------------|-----------|-----------------------------------|
| SERMs | (+) | + | + | + | (+) | |
| | (+) | + | + | + | | |
| Als | + | (+) | | | | (+) |
| SERD | | | | | | |
| Goserelin | (+) | + | | | | |

Nebenwirkg. / Toxizitäten von Bone Modifying Agents (BMA): Bisphosphonate (BP), Denosumab (DB)

**Oxford
LoE**

- **Nierenfunktionsstörungen durch iv Amino-BP** **1b**
- **Kieferosteonekrose (ONJ) typisch unter iv BP und DB (ca. 2%)** **1b**
- **Akute-Phase-Reaktion (iv Amino-BP und DB) 10-30%** **1b**
- **Gastrointestinale Nebenwirkungen (orale BP) 2-10%** **2b**

Bei adjuvanter Bisphosphonattherapie wurden, außer Akute-Phase-Reaktionen, keine gravierende Nebenwirkung gesehen.

Empfehlungen zur Prävention von Kieferosteonekrosen (ONJ)

Oxford LoE: 4

GR: C

AGO: +

- **Unter Bisphosphonattherapie Vermeidung elektiver Zahnbehandlungen mit Manipulationen am Kieferknochen. Falls unvermeidbar wird der prophylaktische Einsatz von Antibiotika empfohlen (LoE 2b)**
- **Zahnsanierung vor einer Bisphosphonattherapie, falls möglich (LoE 2b)**
- **Information der Patientinnen über ONJ-Risiko und Instruieren über Frühsymptome**
- **Bei hohem ONJ-Risiko, Anwendung oraler Bisphosphonate**

Unter adjuvanter Bisphosphonattherapie ist das Risiko für Kieferosteonekrosen gering

Häufige Nebenwirkungen unter Behandlung mit Bisphosphonaten

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| Drug | Akute Phase Reakt. | Renal Tox. | Obere GI-NW | Diar- rhoe | ONJ | |
|----------------------------------|--------------------------|---------------|----------------|---------------|----------|---------------------------|
| Clodronate 1500 i.v. | 0 | + | 0 | 0 | 0 | |
| Clodronate 1600 p.o. | 0 | 0 | + | + | 0 | Non-A |
| Ibandronate 50 mg p.o. | 0 | 0 | + | 0 | 0 | Amino |
| Ibandronate 6 mg i.v. | + | 0 | 0 | 0 | + | |
| Zoledronate 4 mg i.v. | + | + | 0 | 0 | + | |
| Pamidronate 90 mg i.v. | + | + | 0 | 0 | + | |
| Zoledronate 4 mg i.v. q6m | 0 | 0 | 0 | 0 | 0 | |
| Denusomab 120 mg sc q4w | 0 | 0 | 0 | + | + | Hypo- calcemia |

Nebenwirkungen – Small Molecules / Antikörper

Oxford / AGO LoE / GR

Trastuzumab

- Kardiotoxizität in der Adjuvanz (0,8–2,0%)
- Troponin I als Marker für Kardiotoxizität

1b A

2b B

Pertuzumab

- Ekzem, Diarrhoe, Mukositis

2b B

T-DM1

- Thrombozytopenie, Anstieg Leberenzyme
Fieber, Kopfschmerzen, Pneumonitis

2b B

Lapatinib

- Diarrhoe, Ekzem, Fatigue

1b A

Bevacizumab

- Hypertonus, linksventrikuläre Dysfunktion
Blutung, Proteinurie

1a A

Everolimus

- Pneumonitis, Stomatitis, Hyperglycämie,
Infektionen, Ekzem, Thrombozytopenie

2b B



Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Supportive Therapie



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- **Version 2002:**
Diel
- **Versionen 2003–2013:**
**Bauerfeind / Bischoff / Costa / Dall / Diel
/ Fersis / Hanf / Heinrich / Jackisch /
von Minckwitz / Oberhoff / Rody /
Schaller / Scharl / Schütz**
- **Version 2014:**
Schmidt / Möbus

Leitlinien – Umfeld

Nationale und internationale spezifische Leitlinien befassen sich mit verschiedenen Aspekten der evidenzbasierten supportiven Therapie von Karzinompatientinnen und -patienten

Ohne Anspruch auf Vollständigkeit werden derartige (bes. deutsche) Leitlinienwerke genannt.

Hier soll insbesondere auf die Aspekte Wert gelegt werden, die Brustkrebspatientinnen betreffen

**Hingewiesen sei auf die „Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG:
<http://www.onkosupport.de>“**

In Vorbereitung sind die interdisziplinären Leitlinien der AWMF:
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, angemeldet 1.7.2012, gepl. Fertigst.: 30.6.2015
„Palliativmedizin“, angemeldet 03.12.2010, gepl. Fertigst.: 31.03.2014

Anämie – Indikationen für den Einsatz von Erythropoese-stimulierenden Faktoren (ESF)

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|------------|
| ➤ Indiziert bei asymptomatischer Anämie | 1a | B | - |
| ➤ Bei dosisdichter / dosiseskalierter CT (iddETC) | 1b | A | + |
| ➤ Indiziert bei symptomatischer Anämie | 1b | A | + |
| ➤ Adjuvante Situation | 1b | A | + |
| ➤ Neoadjuvante/metastasierte Situation | 1a | A | +/- |
| ➤ Therapie und sekundäre Prophylaxe bei CT-induzierter Anämie (CIA) | 1a | A | + |
| ➤ Verbesserung der Prognose (krankheitsfreies Intervall, Gesamtüberleben) | 2b | B | -- |
| ➤ Therapie beginnt bei Hb-Werten < 10 g/dL | 1a | A | + |
| ➤ Ziel-Hb 11–12 g/dL | 1a | A | + |
| ➤ ESF erhöht das Risiko von thromboembolischen Komplikationen | 1a | A | |

Praktischer Umgang mit ESF

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|------------|
| ➤ Epoetin α und Darbepoetin sind äquieffektiv | 1b | A | ++ |
| ➤ Dosierungen: | | | |
| ➤ Epoetin α: 150 IU/kg 3 x wöchentlich s.c. oder 40.000 IU 1 x / Woche s.c. | 1a | A | ++ |
| ➤ Epoetin α: 80.000 IU alle 2 Wochen s.c. oder 120.000 IU alle 3 Wochen s.c. | 1b | B | + |
| ➤ Darbepoetin: 2,25 μg/kg s.c. wöchentlich | 1b | A | ++ |
| ➤ Darbepoetin: 500 μg s.c. alle 3 Wochen | 1b | A | ++ |
| ➤ Hb-Messungen wöchentlich | | | |
| ➤ Dosisreduktion bei Hb-Anstieg > 1 g/dl innerhalb von 2 Wo. | | | |
| ➤ Dosissteigerung bei Hb-Anstieg < 1 g/dl innerhalb von 4-6 Wo. | | | |
| ➤ Bei FED Eisensubstitution i.v. | 1a | B | + |
| ➤ p.o. Eisensubstitution | 1a | B | +/- |
| ➤ Abbruch der ESF-Gabe bei ausbleibendem Hb-Anstieg nach 9 Wo. | 1b | A | ++ |

Relevante Leitlinien

- Rodgers GM und Gilleath JA: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2013
Available from: URL: <http://www.nccn.org>
- Rizzo JD et al: ASCO/ASH/Clinical Practice Guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 2010; 28: 4996–10

Infektionsprophylaxe

NB nur selten für solide Tumoren wie MaCa anwendbar
 ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

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- **Vermeidung von besonders infektionsbegünstigenden Faktoren/Umgebungen**
- **Prophylaktische Therapie in Low-Risk-Patienten**
- **Prophylaktische Therapie in Hochrisikopatienten* (z.B. gemäß NCCN-Leitlinien) mit:**
 - **Antibiotika**
 - **Antimykotika (Triazol-Antimykotika)**
 - **Virostatika bei soliden Tumoren**
 - **Granulopoese-stimulierende Faktoren**

**Oxford / AGO
 LoE / GR**

5 D +

1a B -

1a A ++

1a B +/-

5 D -

1a A ++

* Definition Hochrisiko: vermutete Neutropeniedauer $< 100/\mu\text{l} \geq 7\text{d}$

Relevante Leitlinien

- Flowers et al: Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 31: 794-810, 2013

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www.ago-online.de

Further
Information

References

Mukositis

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

- **Desinfizierende / entzündungshemmende Maßnahmen:**
Mundspülung mit Kamille- oder Salbeitee bzw. Kamillenextrakt, äther. Öle, Iod-Polyvidon, Hexetidin. Pinselungen mit Kristallviolettlösung 0,5% (Rezeptur) oder Myrrhentinktur, H. Mometasonfuroat + Propylenglykol
- **Schleimhautschützende Maßnahmen (während / nach Zytostatikaapplikation):**
Lutschen von Eiskügelchen (bes. geeignet: Ananassaft, über die Apotheke beziehbar) während 5-Fluorouracil- oder HD-Melphalan-Infusion. Calciumfolinat (Leucovorin-Mundgel®, H) bei HD-Methotrexat: frühestens 24 Stunden nach Ende MTX-Infusion beginnen (sonst Wirkungsverlust des Zytostatikums!), 4- bis 6-stündlich. Dexpanthenol (Panthenol®-Lsg. 5%, H) mehrmals täglich zur Mundspülung.
- **Lokale antimykotische Therapie:**
Amphotericin B, Nystatin, Fluconazol
- **Lokale antivirale Therapie**
Aminoquinurid/ Tetracain-HCl, Aciclovir
- **Lokalanästhetika:**
Orale Anwendung von Benzocain

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Granulozyten-Kolonie stimulierende Faktoren

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- **Primäre Prophylaxe für eine zu erwartende febrile Neutropenie (FNP)**
 - **Bei Risiko für FNP 10–20 %**
 - Im Falle zusätzlicher individueller Risiken
 - **Bei FNP-Risiko > 20 % (e.g. DAC, dosisdichte CT)**
- **Sekundäre Prophylaxe während der Chemotherapie (frühere FNP oder Neutropenie Grad IV > 7 Tage)**
- **Therapeutischer Nutzen der FNP**
- **Beginn der Therapie in Verbindung mit Art und Dauer der Chemotherapie**
 - **Pegfilgrastim Tag 2**
 - **Lipegfilgrastim Tag 2**
 - **Filgrastim/Lenograstim von Tag 2–5 bis absolute Neutrophilenzahl > 2–3 x 10⁹**

1b B +/-

3b C +

1a A ++

1b B ++

1a A +/-

1b A ++

1b B +

1b A ++

Relevante Leitlinien

- Crawford et al: Myeloid Growth Factors. J Natl Compr Canc Netw:1266-1290, 2013
- Smith et al: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors. J Clin Oncol 24:3187-3205, 2006
- Crawford et al: Hematopoietic growth factors. Ann Oncol 21 (suppl 5): v248-v251, 2010

Management febrile Neutropenie

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)

Definition (orale Temp. $>38,5^{\circ}\text{C}$ oder zwei konsekutive Messungen $>38^{\circ}\text{C}$ über 2 h in einer Patientin mit einem $\text{ANC} < 500 \text{ cells/mm}^3$ oder erwarteter Abfall $< 500 \text{ cells/mm}^3$)

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| | | | |
|---|-----------|----------|------------|
| ➤ Klinische Untersuchung | 5 | D | ++ |
| ➤ Tägliche Kontrollen | 5 | D | ++ |
| ➤ Hospitalisierung von Hochrisikopatienten | 1b | A | ++ |
| ➤ Ambulante Therapie bei Niedrigrisikopat. möglich | 1b | A | + |
| ➤ Differentialblutbild | 5 | D | ++ |
| ➤ Blutkulturen | 5 | D | ++ |
| ➤ Bildgebung der Lunge | 3 | C | ++ |
| ➤ Sofortige empirische antibiot. Therapie | 1a | A | ++ |
| ➤ Empirische antimykotische Therapie 4-7d bei keiner Besserung unter Antibiose | 1b | A | ++ |
| ➤ GCSF als therapeutische Maßnahme | 2b | B | +/- |

Empirische Antibiotikatherapie

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Die Empfehlungen zur empirischen Antibiotikatherapie unterliegen einem infektionsbiologisch bedingten Wechsel und bedürfen der beständigen fachkundigen Anpassung.

Die Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de gibt aktuelle Hinweise.

Dexrazoxane

http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

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|--|--------------------------|---|-----|
| ➤ Therapie von Anthrazyklin-Paravasaten | 2b | B | + |
| ➤ In Kombination mit Anthrazyklinen zur Kardioprotektion | 1a | B | +/- |
| ➤ Bei bestehenden kardialen Risiken | | | |
| ➤ Dexrazoxane | 1b | B | + |
| ➤ Alternative Chemotherapie erwägen (Anthrazyklin-frei, liposomal) | 5 | D | ++ |

Paravasate Dexrazoxan

Tag 1: 1.000 mg/m² (max. 2.000 mg), i.v. 1-2 h

Tag 2: 1.000 mg/m² (max. 2.000 mg), i.v. 1-2 h

Tag 3: 500 mg/m² (max. 1.000 mg), i.v. 1-2 h

In anderen Fällen bzw. in denen eine Therapie mit Dexrazoxan nicht indiziert ist, gelten für die Anthrazyklin-Paravasate die folgenden Maßnahmen.

1. Lokale Kälte: Eispackung 6-stündlich jeweils für 15 Min. für 3 Tage
oder: 24 h Abdeckung mit Eisbeuteln
2. Lokale Applikation von Dimethylsulfoxid (DMSO) 99% mit Watteträger 3- bis 4-stündlich für mind. 3 Tage (besser 14 Tage) auftragen und an der Luft trocknen lassen. Das Intervall kann ab Tag 4 auf 6 Stunden verlängert werden.

Antiemetische Therapie

<http://www.mascc.org/antiemetic-guidelines>

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| | | | |
|---|-----------|----------|-----------|
| ➤ Abschätzen des emetogenen Potenzials des jeweiligen Chemotherapie-Protokolls | 5 | D | ++ |
| ➤ Neurokinin-1-Rezeptor-Antagonisten | 1b | A | ++ |
| ➤ Dexamethason | 1a | A | ++ |
| ➤ 5-HT₃-Antagonisten | 1b | A | ++ |
| ➤ Metoclopramid | 3b | C | + |

MASCC/ESMO Antiemetic Guideline 2011



Multinational Association of Supportive Care in Cancer

Organisation und Vorstand:

Richard J. Gralla, MD

Fausto Roila, MD

Maurizio Tonato, MD

Jørn Herrstedt, MD

Supportive Therapie

Antiemetika

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| Wirkstoffgruppe | Substanz | Dosierung | Nebenwirkungen | Potenzial |
|---|-----------------------|---|--|-----------|
| Serotoninantagonisten | Ondansetron | 8 mg i.v., 2 x 4-8 mg p.o | Kopfschmerzen, Diarrhoe, Flushsymptomatik | sehr hoch |
| | Tropisetron | 5 mg i.v., 5 mg p.o. | Transaminasenanstieg | |
| | Granisetron | 1-3 mg i.v. | Darmatonie in hoher Dosierung | |
| | Palonosetron | 0, 25 mg i.v. | | |
| NK 1-Antagonisten | Aprepitant | 125 mg d1, 80 mg d 2-3 p.o. | Cytochrom-P-450- Aktivierung mit Dosisreduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid | sehr hoch |
| | Fosaprepitant | 150 mg d1 i.v. | | |
| Dopaminantagonisten/ substituierte Benzamide | Metoclopramid | bis zu 120 mg/24h als Dauerinfusion od. als Tropfen | Dyskinesien (Antidot:Biperiden) | hoch |
| | Alizaprid | bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.) | Angstreaktion, Depressionen, Diarrhoe | |
| Phenothiazine/ Butyrophenone | Haloperidol | 1-3 mg 4 x/d | Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung | mäßig |
| Corticosteroide | Dexamethason | 8-20 mg i.v. 1-3 x/d | Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg | mäßig |
| | Prednisolon | 100-250 mg i.v. 1-3 x/d | | |
| Benzodiazepine | Diazepam Lorazepam | bis zu 20 mg/d 0,5-1,0 mg/d | Sedation, Atemdepression | gering |
| Antihistaminika | Dimenhydrinat | bis zu 3 x 50 mg/d | Sedation, Mundtrockenheit | gering |

Schmerztherapie

(siehe auch spezifische Leitlinie für Schmerztherapie
www.dgss.org)

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➤ Nicht-Opioide; WHO Stufe 1

Diclofenac resinat, Ibuprofen und / oder Metamizol, Paracetamol

➤ Niedrig-potente Opioide; WHO Stufe 2

Tramadol (vorzugsweise als Retard-Tabletten) bzw. Tilidin/
Naloxon (ebenfalls als Retard-Tabletten)

➤ Hoch-potente Opioide; WHO Stufe 3

Morphin, Buprenorphin (sublingual oder als transdermales System), Fentanyl (transdermales System), Hydromorphon, Oxycodon, als Reserve Levomethadon. Die notwendige Opioiddosis wird schrittweise gegen den Schmerz titriert.

➤ Koanalgetika

Gabapentin, Pregabalin, Carbamazepin, Amitriptylin,
Bisphosphonate

Diarrhoe

➤ Adsorbantien

- Carbo medicinalis , *Kaolin / Pektin, Al-Mg-Silikathydrat*

➤ Analgetica, Opioide

- Loperamid *Codein* , *Morphin i.v.* , *Tinktura opii*,
Butylscopolamin

➤ Pseudomembranöse Kolitis

- Metronidazol *oder bei Versagen Vancomycin*

Obstipation

Wichtige Nebenwirkung einer Opiattherapie

➤ Quellmittel

- Flohsamen, Leinsamen (geschrotet)

➤ Osmotisch wirksame Laxanzien

- Macrogol > Lactulose (Cochrane Review **LoE 1a AGO +**)
- Orale Kontrastmittel: Ultima ratio z.B. Natriumamidotrizoat
- Sorbit

➤ Stimulierende Laxanzien

- Sennesfrüchte, Rizinusöl, Bisacodyl, Natriumpicosulfat

➤ Stuhlweichmacher

- Gleitmittel z.B. Paraffin

➤ Opiod-Rezeptorantagonist bei Opiatobstipation

- Methylnaltrexone

Palliative Care

- “...expert consensus that **combined standard oncology care and palliative care** should be **considered early in the course of illness** for **any patient with metastatic cancer and/or high symptom burden.**”¹
- “Palliative care should be **initiated by the primary oncology team** and augmented by **collaboration** with an interdisciplinary team of palliative care experts.”²
- “Expert **palliative care**, including effective control of pain and other symptoms, **should be a priority.**”³

¹ Smith et al, J Clin Oncol 30 880-887, 2012

² Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012

³ Cardoso et al, Breast 21:242-252, 2012

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Brustkrebs: Spezielle Situationen

Brustkrebs: Spezielle Situationen

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- **Version 2005-2013:**
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/ Harbeck / Huober / Janni / Loibl / Lück /
Lux / Maass / Mundhenke / Oberhoff /
Rody / Scharl**

- **Version 2014:**
Fehm / Schneeweiss

Brustkrebs: Spezielle Situationen

- **„Junge“ Patientin**
- **Brustkrebs in der Schwangerschaft**
- **„Ältere“ Patientin**
- **Mammakarzinom des Mannes**
- **Inflammatorisches Mammakarzinom**
- **Okkultes Karzinom CUP („Cancer of Unknown Primary“)**
- **Morbus Paget**
- **Maligner Phyllodes-Tumor**
- **Sarkome**

Brustkrebs bei der jungen Patientin ≤ 35 Jahre

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- **Ungünstige Tumorbilogie mit schlechter Prognose**
- **Vorteil durch adjuvante Chemotherapie**
- **Vorteil durch endokrine Therapie**
- **Antihormonelle Therapie (TAM) wenn möglich über 5–10 Jahre**
- **Vorteil durch HER2-zielgerichtete Therapie**
- **Vorteil durch temporäre Amenorrhoe nach adjuvanter Chemotherapie (chemotherapie-induziert oder GnRHa-bedingt)**
 - GnRHa als ovarielle Protektion 2 Wochen vor CHT
- **Operation wie bei ≥ 35 Jahre (BET)**
- **Stadien II und III Vorteil durch BW-Bestrahlung**
- **Genetische Beratung und Fertilitätsberatung**

**Oxford / AGO
LOE / GR**

| | | |
|-----------|----------|-------------|
| 2a | B | |
| 1b | A | ++ |
| 1b | A | ++ |
| 1b | B | ++ |
| 2b | B | ++ |
| 2b | B | +/-* |
| 1a | A | -* |
| 2b | B | + |
| 2b | C | + |
| 2b | B | ++ |

***Studienteilnahme empfohlen**

Brustkrebs in der Schwangerschaft*

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- | | | | |
|---|---|---|-----|
| ➤ Diagnostik und Biopsie, wie außerhalb der Schwangerschaft (keine MRT Indikation) | 4 | C | ++ |
| ➤ Staging: Ultraschall, Röntgen-Thorax, wenn indiziert | 5 | D | +/- |
| ➤ OP wie bei Nicht-Schwangeren | 4 | C | ++ |
| ➤ Sentinel-Node Biopsie (nur Technetium) | 4 | C | + |
| ➤ SNB im 1. Trimester | 5 | D | +/- |
| ➤ Sensitivität und Spezifität sind unklar (während Stillzeit); Stillen sollte für 24 Stunden vermieden werden | 4 | C | ++ |
| ➤ Farbstoffblau (keine Studiendaten in der Schwangerschaft) | 4 | C | -- |

* Teilnahme an Registerstudie empfohlen

Brustkrebs in der Schwangerschaft*

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| | | | |
|---|-----------|----------|-----------|
| ➤ Bestrahlung während der Schwangerschaft | 4 | C | - |
| ➤ (Neo-)adjuvante Chemotherapie nur nach erstem Trimester (Indikation wie bei Nicht-Schwangeren) | | | ++ |
| ➤ AC, FA (FEC) | 2b | B | ++ |
| ➤ Taxane | 2b | B | + |
| ➤ MTX (e.g. CMF) | 4 | D | -- |
| ➤ Endokrine Therapie | 4 | D | -- |
| ➤ Anti-HER2-Therapie | 3a | C | -- |
| ➤ Bisphosphonate | 4 | D | - |

Brustkrebs in der Schwangerschaft*

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- | | | | |
|--|-----------|----------|-----------|
| ➤ Entbindung erst bei ausreichender kindlicher Reife | 2b | C | ++ |
| ➤ Eine Beendigung der Schwangerschaft verbessert den mütterlichen Erkrankungsverlauf nicht | 3b | C | |
| ➤ Entbindungsmodus wie bei gesunder Schwangerer; Entbindung ≤ 3 Wochen nach Chemotherapie sollte vermieden werden | 4 | C | ++ |
| ➤ Sollte eine Systemtherapie nach der Entbindung fortgeführt werden müssen, kann Stillen evtl. kontraindiziert sein (cave: Toxizität !) | 5 | D | ++ |

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**FORSCHEN
LEHREN
HEILEN**

*** Teilnahme an Registerstudie empfohlen**

Brustkrebs während Schwangerschaft / Stillperiode*: Prognose

**Oxford
LoE**

➤ Mammakarzinom während Schwangerschaft / Stillzeit

- Prognose wird nicht verschlechtert, wenn korrekte Behandlung

3a

➤ Schwangerschaft / Laktation nach Mammakarzinom

- Prognose wird nicht verschlechtert

3a

Geriatrische Einschätzung

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- **Spezifische Algorithmen nicht existent**
- **Toleranz gegenüber onkologischen Behandlungen variiert erheblich („funktionelle Reserve“)**
- **Zur umfassenden geriatrischen Einschätzung (CGA) gehört die multidisziplinäre Auswertung der Prädiktoren für Morbidität und Mortalität älterer Menschen**
 - **Physische, mentale und psychosoziale Gesundheit**
 - **Basisaktivitäten des täglichen Lebens (Ankleiden, Körperpflege, Zubereiten des täglichen Essens, Medikamenteneinnahme, etc.)**
 - **Lebensumstände, soziales Netz, Verfügbarkeit von Hilfsdienstleistungen**
- **Einschätzungsinstrumente:**
 - **Charlson Comorbidity Index (breit eingesetzt; verlässliche Prädiktion über 10 Jahre)**
 - **12 Prognosefaktoren zur Abschätzung des 4-Jahre-Sterberisikos**
 - **Kurze Screening-Tests (eher zur qualitativen Bewertung geeignet)**
 - **IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale), G-8 Screening tool**

Behandlung der „rüstigen älteren“ Patientin

(Lebenserwartung > 5 Jahre und akzeptable Komorbidität)

Oxford / AGO
LOE / GR

➤ **Bestimmung des aktuellen Gesundheitszustandes**

2b B ++

➤ **Behandlung gemäß Standard**

2a C ++

➤ **Operation wie bei „jüngeren“ Patientinnen**

2b B ++

➤ **Hormontherapie (endokrin-sensibles Ca)**

1a A ++

➤ **Chemotherapie**

➤ **< 70 Jahre**

1a A +

➤ **> 70 Jahre**

2a C +*

➤ **Radiotherapie**

1a A +

➤ **Verzicht auf Radiotherapie in low risk, wenn endokrine Therapie geplant ist****

1b^(a) B +

➤ **Trastuzumab**

2b C +

** low risk, hormonsensibler Tumor und endokrine Behandlung (AI oder Tam); CAVE erhöhtes Lokalrezidivrisiko

* **Studienteilnahme wird empfohlen**

Therapie der „gebrechlichen älteren“ Patientin

(Lebenserwartung < 5 Jahre, erhebliche Komorbiditäten)

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LOE / GR

- | | | | |
|--|-----------------------|----------|-----------|
| ➤ Reduzierte Standardtherapie | 2b | C | ++ |
| ➤ Therapieoptionen abgeleitet aus Studien mit älteren Patientinnen: | | | |
| ➤ Keine Brustoperation (endokrine Therapieoption erwägen) | 2b | C | + |
| ➤ Keine Axilla-Op. (≥ 60 Jahre, cN0, Rez. pos.) | 2b | B | + |
| ➤ Keine Radiatio (≥ 65 Jahre, pT1, pN0, Rez. pos.) | 1b^a | B | ++ |
| ➤ Hypofraktionierte Radiatio | 2b | C | + |
| ➤ Keine Chemotherapie ≥ 70 Jahre bei negativer Risiko-Nutzen-Abwägung | 2b | C | + |

Mammakarzinom des Mannes: Diagnostik und lokale Therapie

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- **Diagnostische Aufarbeitung wie bei Frauen**
 - **Mammographie**
 - **Ultraschall**
- **Standard-Op: Mastektomie**
 - **BET (Tumor-Brust-Relation!)**
 - **Sentinel-Node Biopsie (SNE)**
- **Radiotherapie wie bei Frauen**
(beachte Tumor-Brust-Relation!)
- **Genetische Beratung, falls ein weiterer Verwandter / Verwandte betroffen**
- **Vorsorgeuntersuchung für Zweitkarzinome nicht vergessen (gemäß Richtlinien)**

Oxford / AGO

LOE / GR

| | | |
|-----|---|-----|
| 4 | C | + |
| 3b | C | +/- |
| 2b | B | ++ |
| 4 | C | ++* |
| 4 | C | + |
| 2b | B | + |
| 4 | C | + |
| 2b | B | ++ |
| GCP | | ++ |

* Teilnahme an Registerstudie wird empfohlen

Mammakarzinom des Mannes: Systemtherapie

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- | | | | |
|--|-----------|----------|------------|
| ➤ Adjuvante Chemotherapie wie bei Frauen | 2a | B | ++ |
| ➤ HER2 zielgerichtete Therapie | 5 | D | +* |
| ➤ Endokrine Therapie | 4 | D | ++ |
| ➤ Tamoxifen | 2b | B | ++ |
| ➤ Aromataseinhibitoren (adjuvant) | 2b | B | -* |
| ➤ Aromataseinhibitoren (metastasiert) | 4 | C | +/- |
| ➤ GnRHa + AI (metastasiert) | 4 | C | +* |
| ➤ Fulvestrant (metastasiert) | 4 | C | +/- |
| ➤ Palliative Chemotherapie wie bei Frauen | 4 | C | ++ |

* Studienteilnahme empfohlen

Primäres inflammatorisches Mammakarzinom (IBC, cT4d)

**Oxford / AGO
LOE / GR**

- Stadium cT4d definiert durch invasive Komponente in der Mamma und klinische Zeichen einer Inflammation (z.B. $\geq 1/3$ der betroffenen Brust) ++
- Staging 2c B ++
- Hautbiopsie (mind. 2; Detektionsrate jedoch < 75%) 2c B +
- Präoperative Chemotherapie 2c B ++
 - Regime wie nicht inflammatorisches MaCa
 - Anthrazyklin- und Taxan-basiert 2b B ++
 - Bei HER2 + Hinzunahme von Trastuzumab 2b B ++
- Mastektomie nach Chemotherapie 2c B ++
 - Brusterhaltende Therapie im Fall von pCR 2b C +/-
 - Sentinel-Node-Biopsie alleine 3b C - -
- Radiotherapie 2c B ++
- Postoperative Systemtherapie wie nicht inflammatorisch 4 C ++

Axilla-Metastasen bei unbekanntem Primärtumor (CUP)

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- **Mammographie / Mamma-Ultraschall (MG / MS)**
- **Mamma-MR**
- **Staging (CT Thorax / Abdomen, Schilddrüsen-Sonographie, HNO-Untersuchung)**
- **PET / PET-CT**
- **Genexpressionsprofile**
- **ER, PgR, HER2**
- **Axilladisektion**
- **Systemtherapie entsprechend N+ Mamma-Ca**
- **Mastektomie bei unauffälligem MRT**
- **Brust-Bestrahlung bei negativem Mamma-MRT**
- **Bestrahlung der regionären LK entsprechend Mammakarzinom-LL**

**Oxford / AGO
LOE / GR**

| | | |
|-----------|----------|------------|
| 3 | B | ++ |
| 3 | B | ++ |
| 3 | B | ++ |
| 3b | B | +/- |
| 2c | B | +/- |
| 5 | D | ++ |
| 3a | C | ++ |
| 3a | C | ++ |
| 3a | C | - |
| 3b | C | +/- |
| 3b | B | + |

Morbus Paget der Mamille

**Oxford / AGO
LOE / GR**

- **Histologische Sicherung** **++**
- **Mammographie, Mammasonographie** **4 D ++**
 - **Mamma-MR, falls andere Bildgebung negativ** **4 C +**
- **Operation einschließlich Exzision des NAC (R0)** **1c B ++**
 - **Weite Exzision (wie bei DCIS) + Bestrahlung** **2b B +**
 - **Sentinel-Lymphknoten-Exzision (SNE)** **2b B +/-**
- **Morbus Paget mit Mamma-Tumor
(invasives MaCa, DCIS)**
 - **Therapie entsprechend Standards der
Grunderkrankung** **5 D ++**
- **Isolierter Morbus Paget des NAC (< 5 %):**
 - **R0-Resektion, keine adjuvante Bestrahlung** **4 D ++**

Maligner Phylloiddtumor

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**Oxford / AGO
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- | | | | |
|---|-----------|----------|------------|
| ➤ Komplette (weite!) lokale Exzision oder einfache Mastektomie | 2b | B | ++ |
| ➤ SNE / Axilladisektion bei cN0 | 4 | C | -- |
| ➤ Staging | 5 | D | ++ |
| ➤ Systemische adjuvante Therapie (Chemotherapie, endokrine Therapie) | 4 | C | -- |
| ➤ Adjuvante Radiotherapie | 4 | C | -- |
| ➤ Bei T ≥2 cm (BET) oder T ≥10 cm (Mastektomie) | 2b | C | +/- |
| ➤ Therapie des Lokalrezidivs | | | |
| ➤ R0-Resektion | 4 | C | ++ |
| ➤ Radiotherapie, Chemotherapie nach R1-Resektion | 4 | C | +/- |
| ➤ Fernmetastasen (sehr selten) | | | |
| ➤ Therapie wie bei Weichteilsarkomen | 4 | C | ++ |

Sarkome / Angiosarkome der Brust (Cave: sehr aggressiv!)

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Therapie der Primärerkrankung:

- **MG/ MS zur Bestimmung der Tumorausdehnung**
- **Präoperative MRT zur Bestimmung der Tumorausdehnung**
- **Diagnose durch Stanzbiopsie**
- **Diagnose durch Feinnadelbiopsie**
- **Staging**
- **Prognostische Faktoren: Größe, Grading, Tumorränder**
- **Operation mit weiten freien Tumorrändern**
 - **Brusterhaltende Therapie**
- **Axilläre Dissektion im Falle cN0**
- **Adjuvante Chemotherapie, Radiotherapie**
 - **Adjuvante Chemotherapie (anthrazyklin-basiert), Radiotherapie im Falle hohes Risiko (Grade II-III, Größe > 5 cm, R1)**

Therapie des Lokalrezidivs:

- **R0-Resektion**
- **Radiotherapie, Chemotherapie nach R1-Resektion**

Fernmetastasierung/ nicht resektable Tumoren:

- **Therapie wie Weichteilsarkome**
- **Paclitaxel weekly / liposomales Doxorubicin (bei Angiosarkomen)**
- **Antiangiogene Therapie**
- **Trabectedin (nach Anthrazyklin / Ifosfamid-Versagen in Leiomyosarkomen)**

Oxford / AGO LOE / GR

| | | |
|----|---|-----|
| 3a | C | -- |
| 3a | C | ++ |
| 3a | C | ++ |
| 3a | C | -- |
| 4 | D | ++ |
| 3a | C | ++ |
| 3a | C | ++ |
| 3a | C | +/- |
| 3a | C | - |
| 3a | C | +/- |
| 4 | C | +/- |
| 4 | C | ++ |
| 4 | C | +/- |
| 4 | C | ++ |
| 2b | B | + |
| 4 | C | +/- |
| 2b | B | + |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Brustkrebs Nachsorge



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Brustkrebs Nachsorge

- **Versionen 2002–2013:**
**Bauerfeind / Bischoff / Blohmer /
Böhme / Costa / Diel / Gerber / Hanf /
Heinrich / Janni / Kaufmann / Kümmel /
Lux / Möbus / Mundhenke / Oberhoff /
Scharl / Thomssen**

- **Version 2014:**
Solomayer / Thomssen

Brustkrebs-Nachsorge

Ziele

**Oxford / AGO
LoE / GR**

- | | |
|--|---------------|
| ➤ Verbesserung der Lebensqualität | 2b B + |
| ➤ Verbesserung der körperlichen Leistungsfähigkeit | 2b B + |
| ➤ Reduktion therapiebedingter Nebenwirkungen (nach OP, Systemtherapie und Strahlentherapie) | 2b B + |

Brustkrebs-Nachsorge Ziele

Oxford / AGO

LoE / GR

- **Re-Evaluation laufender adjuvanter Therapien** **5 D ++**
 - inkl. Überprüfung der Compliance endokriner Therapien
- **Pro-aktive Verbesserung der Compliance anstreben** **++**
durch:
 - Patientenaufklärung über die günstigen Daten einer 5- bis 10-jährigen adj. endokrinen Therapie
 - Frühzeitige Therapie von Nebenwirkungen (z.B. Sportintervention, NSAID, Vitamin D/Calcium-Substitution)

Brustkrebs Nachsorge Ziele

Oxford / AGO

LoE / GR

Früherkennung von heilbaren Rezidiven

- Intramammäre Rezidive **1a B ++**
- Lokoregionäre Rezidive **1a B ++**

Früherkennung von Metastasen

- Früherkennung symptomatischer Metastasen **3b C +**
- Früherkennung asymptomatischen Metastasen **1a A -**

Brustkrebs Nachsorge Ziele

Oxford / AGO

LoE / GR

➤ Psychosoziale Aspekte der Beratung

4 C +

Schwangerschaft, Kontrazeption,
Sexualität, Lebensqualität, Meno-
pausensyndrom, Angst vor Rezidiv

➤ Zweitmeinung zur Primärtherapie

2c B ++

➤ Allgemeine Beratung (z.B. Genetik, HRT)

2c C +

Brustkrebs Nachsorge

Ziele

Interventionen hinsichtlich Begleiterkrankungen und Lebensstil, um einen negativen Einfluss auf den Krankheitsverlauf zu reduzieren.

- **Einstellung Diabetes mellitus (Typ II)**
(> 25% unerkannter DM bei postmenopausalem MaCa)
- **Gewichtsintervention**
(bei BMI <18,5 und >40)
- **Intervention bei Nikotinabusus**
(durch Rauchen 2x erhöhte brustkrebsspezifische, 4x erhöhte nicht-brustkrebsspezifische Mortalität)
- **Moderate Sportintervention bei Bewegungsmangel**
(Rel. Reduktion der Mortalität um bis zu 25%)

Oxford / AGO

LoE / GR

++

2a B +

2b B ++

1b A + +

Nachsorgeziele – von Patientinnenseite gesehen

Oxford LoE 4 C

- **Untersuchung der Brust**
- **Beruhigung und Bestätigung**
- **Führung der Patientinnen, Fragen beantworten**
- **Überprüfung der Behandlung und potenzieller Nebenwirkungen**
- **Psychosoziale Unterstützung**

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Kwast AB et al. Eur J Cancer Care (Engl). 2013 Nov;22(6):754-64.

Ziele der Nachsorge aus der Sicht der medizinischen Betreuer u. Patientinnen

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| | Medizinische Betreuer | Patientinnen |
|----------------------|--|--|
| Häufig erwähnt | Früherkennung von Rezidiven und Zweittumoren | Untersuchung der Brust |
| | Psychosoziale Unterstützung | Beruhigung und Bestätigung |
| | Führung, Information und Überweisung an Fachärzte | Führung der Patientinnen, Beantwortung von Fragen |
| Gelegentlich erwähnt | Überprüfung der Behandlung und potenzieller Nebenwirkungen | Überprüfung der Behandlung und potenzieller Nebenwirkungen |
| | Früherkennung von Metastasen | Psychosoziale Unterstützung |
| | Klinische Studien, Aufbau eigener Datenbanken | |

Nach Kwast AB et al. Eur J Cancer Care (Engl). 2013 Nov;22(6):754-64.

Routine-Nachsorgeuntersuchungen bei asymptomatischen Patientinnen

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Untersuchungen:

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| | | | |
|--|----|---|-----|
| ➤ Anamnese (spezifische Symptome) | 1a | A | ++ |
| ➤ Untersuchung | 1a | B | ++ |
| ➤ Brust-Selbst-Untersuchung | 5 | D | + |
| ➤ Mammographie | 1a | A | ++ |
| ➤ Mammasonographie | 2a | B | ++ |
| ➤ Mamma-MR in der Routine | 3b | B | +/- |
| ➤ Mamma-MR bei unklarer Mammo- graphie / -sonographie | 3b | B | + |
| ➤ Gynäkologische Untersuchung | 5 | D | ++ |

Routine-Nachsorgeuntersuchungen bei asymptomatischen Patientinnen

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|----------|
| ➤ Routinelabor (incl. Tumormarker) | 1a | A | - |
| ➤ Lebersonographie | 1a | A | - |
| ➤ Skelettszintigraphie | 1a | A | - |
| ➤ Thorax-Röntgen | 1a | A | - |
| ➤ CT-Untersuchungen (Thorax, Abdomen und Becken) | 2a | D | - |
| ➤ Detektion isolierter / zirkulierender Tumorzellen | 2a | D | - |
| ➤ PET-CT | 2b | B | - |
| ➤ Ganzkörper-MRT | 2b | B | - |

Früherkennung von potenziell heilbaren Erkrankungen

**Oxford / AGO
LoE / GR**

Lokoregionäre Rezidive (Thoraxwand, intramammäre Rezidive):

- Inzidenz 7–20 % (abhängig von der Zeit der Nachbeobachtung)
- **Brust-Selbst-Untersuchung**
- **Klin. Untersuchung, Mammographie & US**
- **Mamma-MR**

5 D +

1a B ++

3b B +/-

Früherkennung von potenziell heilbaren Erkrankungen

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Kontralaterales Mammakarzinom:

- Rel. Risiko: 2,5–5
- Inzidenz: 0,5–1,0 % / Jahr
- **Brust-Selbst-Untersuchung** 5 D +
- **Klin. Untersuchung, Mammographie & US** 1a A ++
- **Mamma-MR in der Routine** 5 D -

Früherkennung von potenziell heilbaren Erkrankungen

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Sonstige Zweitkarzinome:

Kolorektal RR 3,0; Endometrium RR 1,6
Ovar RR ca. 1,5

- Screening auf Zweitmalignome entsprechend den gültigen Leitlinien ++
- Gyn. Krebsfrüherkennungsuntersuchung 5 D ++
- Routinemäßige transvaginale Sonographie / Biopsie des Endometriums 1b B -

Brustkrebs Nachsorge (inkl. CLIS, DCIS)

Synopsis

Empfehlung für asymptomatische Patientinnen

(mod. nach ASCO-Empfehlungen 2012, NCCN 2.2011 und S3 Leitlinie 2012)

| | | Nachsorge/Follow-Up* | | | | Screening | |
|---|-------------------|---|---|---|---------------------------|-----------|-----------------------------|
| Jahre nach Primärtherapie | | 1 | 2 | 3 | 4 | 5 | > 6 |
| Anamnese, klinische Untersuchung, Beratung | | inv.: alle 3 Mon. | | | inv.: alle 6 Mon. | | inv.: alle 12 Mon. |
| | | CLIS / DCIS: alle 6-12 Monate | | | | | CLIS / DCIS: alle 12 Monate |
| Selbstuntersuchung | | monatlich | | | | | |
| Bildgebende Diagnostik, Laboruntersuchungen | | indiziert nur bei Symptomatik +/- Befunden +/- Verdacht auf Rezidiv/Metastasen | | | | | |
| Mammo- graphie und Sono- graphie | inv.: BET** | ipsilat.: alle 6 -12 Mon. kontralat.: alle 12 Mon. | | | beidseits: alle 12 Monate | | |
| | inv.: Mastektomie | kontralateral alle 12 Monate | | | | | |
| | CLIS / DCIS | alle 12 Monate | | | | | |

* Fortlaufende "Nachsorgeuntersuchungen" bei noch laufender adjuvanter Therapie

** 1. Mammographie nach BET 6-12 Monate nach kompletierter Radiatio

Mammakarzinom Nachsorge. Dauer. „Breast Nurses“.

**Oxford / AGO
LoE / GR**

➤ Dauer der Nachsorge

➤ Bis zu 5 Jahre

1c A ++

➤ Bis zu 10 Jahre

1c A +

➤ Nachsorge durch spezialisierte „Breast nurses“

2b B +/-*

***Studies recommended**

Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients

- **Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.**
- **ER-positive patients have stable risk over many years requiring long term surveillance.**
- **However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.**



Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Loko-regionäres Rezidiv



Loko-regionäres Rezidiv

- **Version 2002:**
Brunnert / Simon
- **Versions 2003–2013:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Lisboa / Mundhenke /
Rezai / Solomayer / Souchon / Thomssen**
- **Version 2014:**
Dall / Maass

Loco-regionäres Rezidiv Inzidenz und Prognose

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| Lokalisation | Häufigkeit (%) | 5-J. Gesamtüberleben (%) |
|---|-------------------|-----------------------------|
| Ipsilaterales Rezidiv¹ (nach BET + Radiatio) | 10 (2–20) | 65 (45–79) |
| Brustwand¹ (nach Mastektomie) | 4 (2–20) | 50 (24–78) |
| Wie oben plus supraklavikuläre LK ² | 34% | 49% (3-J. OS) |
| Axilla: | | |
| Nach ALND¹ | 1 (0.1–8) | 55 (31–77) |
| Nach SNB⁴ | 1 | 93% |
| Multiple Lokalisationen² | 16 (8–19) | 21 (18–23) |

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¹ Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991; ²Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201; ³Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978; ⁴Andersson Y, et al. Br J Surg 99(2):226-31,2012

Loko-regionales Rezidiv Staging

Oxford AGO
LoE / GR

Untersuchungen vor Behandlung:

| | | | |
|----------------------------------|---|---|----|
| ➤ Histologische Sicherung | 5 | D | ++ |
| ➤ Reevaluierung von ER, PR, HER2 | 5 | D | ++ |
| ➤ Komplettes Re-Staging | 5 | D | ++ |

Loko-regionäres Rezidiv

Risikofaktoren bei Primärdiagnose

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Erhöhtes Risiko für ein Lokoregionäres Rezidiv

- Junges Alter
- Positive mikroskopische Ränder
- Unterlassene Strahlentherapie (falls adjuvant indiziert)
- Ausgedehnte intraduktale Komponente
- Gefäßinvasion
- Triple-negativ und HER2+/HR neg. vs. HR pos.
- Grading (G3 vs. G1)
- Erhöhte Proliferationsmarker (z.B. Ki67)
- pT (> 2 vs. ≤ 2 cm)
 - * nodal negativ
- pN (N1 vs. N0)
- Anzahl befallener LK
- Inflammatorisches Mamma-Ca
- Medialer Tumorsitz (vs. zentral/lateral)

Oxford
LoE

1a

1a

1a

1b

1b

2a

1b*

2b

1b*

1a

1a

1a

2b

4

Metaanalysis: TNBC and Local Recurrence

Wang et al., Surg Oncol 2013 (Epub)

n = 15312 BC-patients, 22 studies, Hazard-ratios

| | | | |
|------|------------------|-----|---------------|
| | BCT | vs. | ME |
| ILRR | 0.75 (0.65-0.87) | | |
| DM | 0.68 (0.60-0.76) | | |
| | TNBC-subtype | vs. | other subtype |
| ILRR | 1.88 (1.58-2.22) | | |
| DM | 2.12 (1.72-2.62) | | |
| | TNBC-subtype | vs. | HER2-subtype |
| ILRR | 0.69 (0.53-0.91) | | |
| DM | n.s. | | |

ILRR: ipsilateral locoregional recurrence

DM: distant metastasis

TNBC: triple negative breast cancer

BCT: breast conserving therapy ME: mastectomy

Risk Factors for Locoregional Recurrences after ME

Karlsson et al. Ann Oncol 23:2852-8, 2012

IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence ...:

...>15% chest wall: age <40; ≥ 4 pos. nodes, 0-7 uninvolved nodes

...>10% supraclavicular: ≥ 4 pos. nodes

...>5% axillary failure: age <40; unknown tumor size, 0-7 uninvolved nodes

Metaanalysis: 7174 BCT and 5418 ME

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Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after Breast Cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 133(3):831-41, 2012

After BCT:

HR-positive tumors show a lower risk for LRR than...
triple negative tumors (RR 0.38) and....
HER2-expressing tumors (RR 0.34)

After ME:

HR-positive tumors show a lower risk for LRR than...
HER2- expressing tumors (RR 0.69) and...
triple negative tumors (RR 0.61)

Result:

HR-positive tumors exhibit the lowest rate of local recurrence.

Loko-regionäres Rezidiv

Prognostische / Prädiktive Faktoren

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Risikofaktoren beim Lokalrezidiv für das Auftreten eines Re-Rezidivs

- Tumorgröße 2a B
- Multifokalität 2a B
- Lokalisation 2b B

Risikofaktoren beim Lokalrezidiv für Metastasen/Überleben

- Frühes (<2-3J.) vs. spätes Rezidiv 2b B
- LVSI/Grad/ERneg/knappe Res.ränder
(falls ≥ 2 Faktoren pos.) 3b B

Prädiktive Faktoren für therapeutische Erwägungen

- HER2 2b B ++
- ER and PgR 2b B ++

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

Panet-Raymond V et al., Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. Cancer 117:2035, 2011

n=6020 pat., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:

TTR <48 months

LVSI (of the LRR)

ER negative LR-tumor

high grade

close margins of recurrent tumor

⇒ if ≥ 2 factors positive ⇒ worse OS

Ipsilaterales Rezidiv nach BET

Operative Therapie

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➤ **Mastektomie (Ziel: R0)**

3b B ++

➤ **Re-BEO mit tumorfreien Rändern**

3 C +/-

± Lappen-Rekonstruktion

- Überlebensnachteil kann nicht ausgeschlossen werden
- Schlechtes kosmetisches Resultat
- Verschlechterte lokale Tumorkontrolle

➤ **Axilläre Intervention nach primärer AxDiss, falls cN0**

4 C -

➤ **SNL nach prim. SNL falls cN0***

4 D +/-

➤ **Palliative Operation in der M1-Situation**

5 D +

(z.B. Schmerz, Ulzeration, psychosoziale Indikation)

* Falls kein Sentinel identifiziert wird, sollte keine Axilladisektion erfolgen

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Operative Therapie

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- | | |
|---|-------------------------|
| ➤ Kurative Situation: R0-Resektion | 2b A ++ |
| ➤ Palliative Situation: Resektion tieferer Thoraxwandanteile | 5 D +/- |
| ➤ Palliative Operation bei M1-Situation (z.B. Schmerz, Ulzeration, psychosozial) | 5 D + |

Lokoregionäres Rezidiv nach R0-Resektion – Systemische Therapie

**Nach patho-histologischer Re-Evaluation des
Rezidivtumors (ER, PgR, HER2)**

**Oxford AGO
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- **Endokrine Therapie bei endokrin
responsiblen Tumoren**
- **Chemotherapie (ggfs. neoadjuvant)**
- **Bei HER2- überexprimierenden
Tumoren**

2b B ++

2b B +

Chemotherapie und HER2-zielgerichtete Therapie

5 D +

Chemotherapie bei lokoregionärem Rezidiv

➤ CALOR Trial – Overall Survival

Kein Unterschied bei ER-/ER+
Unabhängiger prognostischer Marker!

Loko-regionäres Rezidiv (R0-Resektion unwahrscheinlich) - Systemische Therapie

**Nach patho-histologischer Re-Evaluation des
Rezidivtumors (ER, PgR, HER2)**

**Oxford AGO
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➤ **Endokrine Therapie bei endokrin
responsiblen Tumoren**

2b B ++

➤ **Chemotherapie (prä-oder postoperativ)**

2b B ++

➤ **Bei HER2-überexprimierenden
Tumoren**

HER2-zielgerichtete Therapie (+ Chemotherapie)

1b A ++

Ipsilaterales Rezidiv nach BET Strahlentherapie

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Nach Re-BEO

- **Ganzbrustbestrahlung**
(falls keine adjuvante RT erfolgt)
- **Erneute Bestrahlung (Mamma)**
(z.B. Brachytherapie, externe Beam RT)

3b C ++

3b C +/-

Nach Mastektomie

- **Thoraxwandbestrahlung +/- regionäre Lymphknoten**
(14% befallene supraklavikuläre LK)
- **Dosiseskalation der Bestrahlung**

2b B +/-

3b C -

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Lokale Behandlung

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Thoraxwandrezidiv nach Mastektomie

- Falls keine Postmastektomie-Bestrahlung erfolgte
 - Kurative Situation: Bestrahlung der Brustwand +/- regionalen LK
- Zweit-Bestrahlung (Thoraxwand + Hyperthermie)

2b B +

1b B +/-

Axilläres Rezidiv

- Bestrahlung der Axilla nach R0-Resektion
 - Keine adjuvante Axillabestrahlung erfolgt
 - Adjuvante Axillabestrahlung erfolgt

3b C +

5 D +/-

Loko-regionäres Rezidiv

Behandlungsoptionen bei nicht kurativen Fällen

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| | | | |
|--|-----------|----------|------------|
| ➤ Topische Chemotherapie (Miltefosin) | 3b | C | + |
| ➤ Begleitende Radio-Chemotherapie | 3b | C | + |
| ➤ Hyperthermie* | | | |
| ➤ In Kombination mit Radiotherapie | 1b | B | + |
| ➤ In Kombination mit Chemotherapie | 4 | C | +/- |
| ➤ Intra-arterielle Chemotherapie | 4 | C | +/- |
| ➤ Photodynamische Therapie | 4 | C | +/- |
| ➤ Elektrochemotherapie | 3b | C | +/- |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Endokrine und zielgerichtete Therapie des metastasierten Mammakarzinoms

START

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Endokrine Therapie des metastasierten Mammakarzinoms

- **Version 2002:**
Gerber / Friedrichs
- **Versionen 2003–2013:**
**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat /
Kaufmann / Loibl / Lück / von Minckwitz /
Müller / Nitz / Schneeweiß / Stickeler**
- **Version 2014:**
Mundhenke / Schütz

Endokrine Therapie des metastasierten Mammakarzinoms

Indikation

Oxford LoE: 1a

GR: A

AGO: ++

Die endokrine Therapie ist die erste Therapieoption in der Behandlung des metastasierten hormonrezeptor-positiven (oder unbekannten) Mammakarzinoms

- **Ausnahme: akute lebensbedrohliche Erkrankung**
- **Cave: Der HR-Status kann sich im Laufe der Erkrankung verändern. Falls möglich, sollte eine Histologie der neuen Metastase gewonnen werden**

Vergleich ER/PgR und HER2 Metastase vs. Primärtumor

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| Publikation | Anzahl der Patienten | Veränderung ER (%) | Veränderung PgR (%) | Veränderung HER2 (%) |
|---------------------|----------------------|--------------------|---------------------|----------------------|
| Prospektiv | | | | |
| Thompson | 137 | 10 | 25 | 3 |
| Amir | 94 | 14 | 40 | 10 |
| Retrospektiv | | | | |
| Lindström | 459 | 33 | 40 | 14 |
| Niikura | 182 | - | - | 24 |
| Jensen | 119 | 12 | | 9 |

Endokrine Therapie der prämenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom

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LoE / GR**

| | | | |
|---|----|---|-----|
| ➤ GnRH-A + Tamoxifen (vs. OFS od. Tam) | 1a | A | ++ |
| ➤ Unterdrückung der Ovarialfunktion (OFS) | 2b | B | + |
| ➤ Tamoxifen | 2b | B | + |
| ➤ GnRH-A. + AI (first + second line) | 2b | B | + |
| ➤ GnRHα + Fulvestrant | 4 | C | +/- |
| ➤ Aromataseinhibitoren ohne OFS | 3 | D | - - |

Endokrine Therapie des HER2 negativen metastasierten Mammakarzinoms

Substanzen für postmenopausale Patientinnen mit adjuvanter Tamoxifen-Vorbehandlung oder ohne adjuvante endokrine Therapie

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| ➤ Aromataseinhibitoren (3rd gen) (> non-AI*) | 1a | A | ++ |
| ➤ Tamoxifen (vs. keine Therapie) | 1a | A | ++ |
| ➤ Fulvestrant 500 mg | 1b | B | ++ |
| ➤ Fulvestrant 250 mg (=AI) | 2b | B | + |
| ➤ MPA/MA (< AI) | 1a | A | +/- |
| ➤ Fulvestrant 250 mg + Anastrozol (vs. Ana) | 1b | B | +/- |

*Es gibt keine Hinweise für die Überlegenheit eines einzelnen Aromataseninhibitors. Um eine spätere Therapie nach Zulassungsstatus mit Everolimus zu ermöglichen, sollte ein nicht-steroidaler AI bevorzugt werden.

Endokrine Therapie bei postmenopausalem HER2 negativem metastasiertem Mammakarzinom nach adjuvant Tamoxifen oder ohne adjuvante endokrine Therapie

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Behandlungssequenz

Oxford / AGO
LoE / GR

| | | | | |
|-----------------------|-----------------------------------|----|---|-----|
| 1 st line: | Aromataseinhibitoren (3rd gen)* | 1a | A | ++ |
| | Fulvestrant 250 mg + Anastrozol | 1b | B | +/- |
| 2 nd line: | Fulvestrant | 1b | B | |
| | Fulvestrant 500 mg | 1b | B | ++ |
| | Fulvestrant 250 mg | 1b | B | + |
| | Exemestan + Everolimus | 1b | B | ++ |
| | Tamoxifen | 3b | C | + |
| | Aromataseinhibitoren** | 2b | B | + |
| | Tamoxifen + Everolimus | 2b | B | + |
| Weitere | MPA/MA | 4 | D | +/- |
| Therapie- | Estradiol 6 mg täglich | 3b | C | +/- |
| Linien: | Re-Induktion vorheriger Therapien | 5 | D | +/- |

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*Es gibt keine Hinweise für die Überlegenheit eines einzelnen Aromataseinhibitors

** Steroidale oder nicht-steroidale in Abhängigkeit vom bisherigen AI

Therapiealgorithmen nach adjuvanter Tamoxifentherapie

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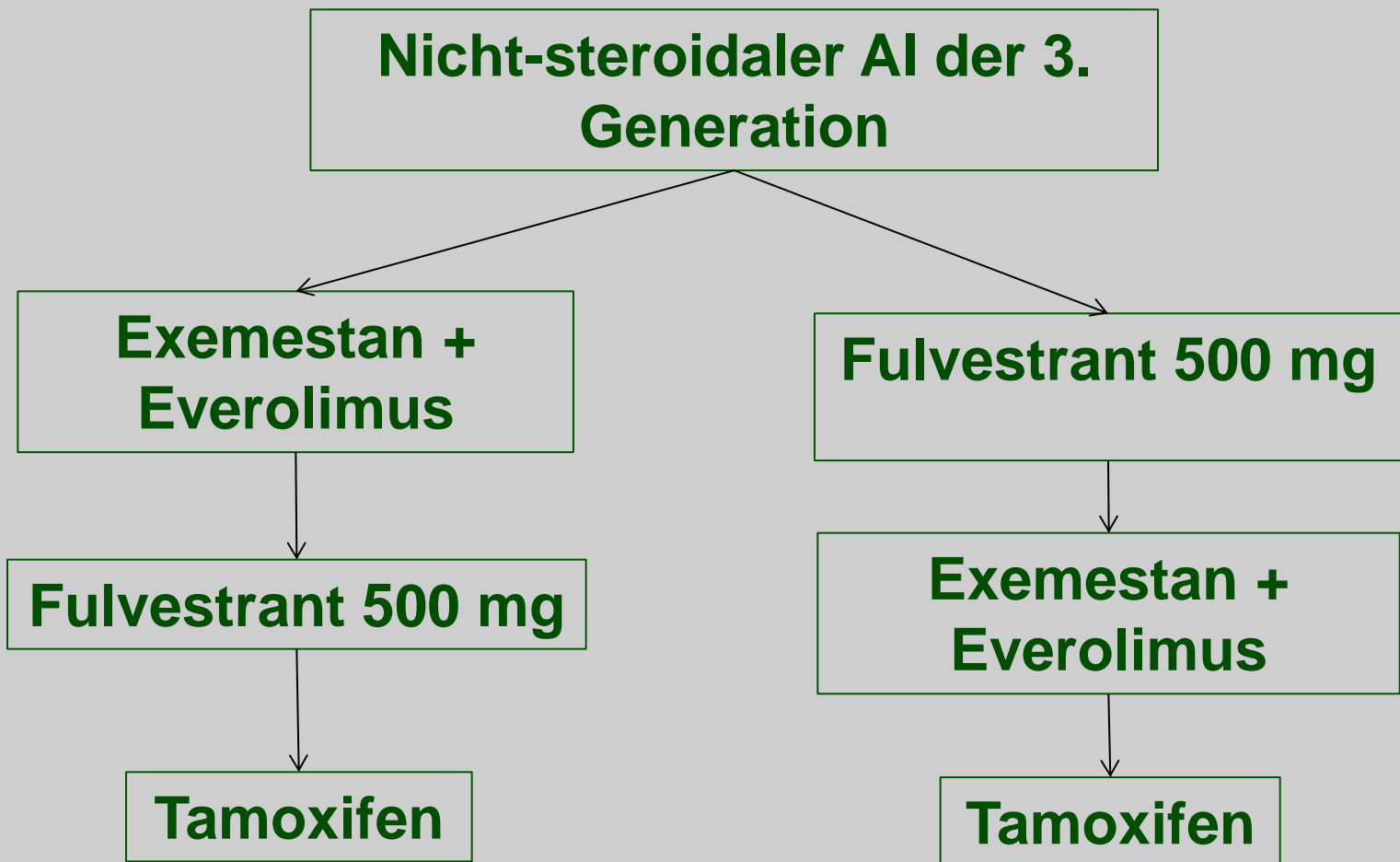
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Further
Information

References

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Endokrine Therapie des postmenopausalen HER2 negativen metastasierten Mammakarzinoms nach adjuvanter Therapie mit einem AI

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Behandlungssequenz

1st line:

- Tamoxifen
- Fulvestrant 500 mg
- Exemestan + Everolimus* (Frührezidiv inn. 12 Mon.)
- steroidaler nach non-steroidalem AI
non-steroidaler nach steroidalem AI
- Tamoxifen + Everolimus

2nd line:

- Fulvestrant 500 mg
- Exemestan + Everolimus*
- Tamoxifen (falls Tam-naiv)
- Tamoxifen + Everolimus

Weitere Linien:

- MPA/MA
- WH einer Vortherapie

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| | | |
|----|---|-----|
| 2b | B | ++ |
| 1b | B | ++ |
| 1b | A | ++ |
| 2b | B | + |
| 2b | B | + |
| 1b | B | ++ |
| 1b | B | ++ |
| 5 | D | + |
| 2b | B | + |
| 4 | C | +/- |
| 5 | D | +/- |

* Nach Vortherapie mit zumindest einem nicht-steroidalen AI (met u/o adjuvant)

Therapiealgorithmen nach adjuvanter AI Therapie

**Kurzes therapiefreies
Intervall ≤ 12 Monate**

**Exemestan +
Everolimus**

Fulvestrant 500 mg

Tamoxifen

**Langes therapiefreies Intervall
>12 Monate**

Fulvestrant 500 mg

Tamoxifen

**Exemestan +
Everolimus**

Tamoxifen

Fulvestrant 500 mg

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HER2 positives und HR-positives metastasiertes Mammakarzinom

Endokrine Therapie

der postmenopausalen HER2 positiven metastasierten Mammakarzinom-Patientin

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| | Oxford / AGO LoE / GR | | |
|-------------------------------------|--------------------------|----------|------------|
| ➤ Anastrozol und Trastuzumab | 1b | B | +/- |
| ➤ Letrozol und Trastuzumab | 2b | B | +/- |
| ➤ Letrozol und Lapatinib | 1b | B | +/- |
| ➤ Fulvestrant and lapatinib | 1b^a | B | - |

**Es sollte in Erwägung gezogen werden, eine
Chemotherapie mit einer anti-HER2-Therapie zu
kombinieren!**

Kombination von anti-HER2-Therapie mit endokriner Therapie

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| Treatment (no. of pats) | PFS (mo) | Response (CBR) | OS (mo) |
|---|---|-------------------|------------------------|
| Trastuzumab + anastrozole vs. anastrozole (n=207) | 4.8 vs. 2.4 (5.6 vs. 3.8 with central confirmed receptor status) | 42.7% vs. 27.9% | 28.5 vs. 23.9 mo; n.s. |
| Trastuzumab + letrozole vs. letrozole (n=57) | 14 vs. 3.3 | 27% vs. 13% | n.r. |
| Lapatinib + letrozole vs. letrozole (n=219/1286) | 8.2 vs. 3.0 | 48% v 29% | 33.3 vs. 32.3 mo |
| Lapatinib + fulvestrant vs fulvestrant (n=267/324) | 5.2 vs. 4.0 (all) 5.9 vs. 2.8 (HER2+) | | 22.3 vs. 21.9 (all) |

Simultane oder sequentielle endokrin-zytostatische Behandlung

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➤ **Simultane endokrin-zytotoxische Therapie**

1b A - -

- **Höhere Ansprechraten ohne Einfluss auf das progressionsfreie und/oder Gesamtüberleben**
- **Erhöhte Nebenwirkungsrate**

➤ **Endokrine Erhaltungstherapie nach Ansprechen auf eine Chemotherapie**

3 C ++

- **Verlängert das progressionsfreie Überleben**

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◀ START

Chemotherapie mit oder ohne zielgerichtete Substanzen beim metastasierten Mammakarzinom

Chemotherapie mit oder ohne zielgerichtete Substanzen bei metastasiertem Mammakarzinom

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- **Version 2002:**
von Minckwitz / Schaller / Untch
- **Version 2003–2013:**
**Bischoff / Dall / Fersis / Friedrichs /
Harbeck / Jakisch / Janni / Möbus / Rody /
Scharl / Schmutzler / Schneeweiss /
Schütz / Stickeler / Thomssen**
- **Version 2014:**
Bischoff / Janni

Chemotherapie

Krankheitsfreies und Gesamtüberleben

**Oxford / AGO
LOE / GR**

- **In retrospektiven Analysen klinischer Studien wurde eine Verlängerung des Überlebens über die Zeit gezeigt** **2a**
- **Ein Überlebensvorteil wurde in einzelnen, prospektiv-randomisierten Studien nachgewiesen** **1b**
- **Mehrere Linien der sequenziellen Therapie sind von Vorteil (gleiche Wirksamkeit, geringere Toxizität)** **1b**
- **Bei bestimmten Kombinationen von einer Chemotherapie mit zielgerichteten Substanzen wurde ein entsprechender Überlebensvorteil festgestellt** **1b**

Therapie des metastasierten Mammakarzinoms

Prädiktive Faktoren

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| Therapie | Faktor | Oxford / AGO LOE / GR | | |
|-----------------------|--|--------------------------|---|----|
| | | | | |
| Endokrine Therapie | ER/PR Rezeptorstatus (Primärtumor, Metastase) | 1a | A | ++ |
| | vorheriges Ansprechen | 2b | B | ++ |
| Chemotherapie | vorheriges Ansprechen | 1b | A | ++ |
| Trastuzumab | HER2 (Primärtumor, besser Metastase) | 1a | A | ++ |
| Bisphosphonate | Knochenmetastasen | 1a | A | ++ |
| Bone modifying drugs | Knochenmetastasen | 1a | A | ++ |
| Beliebige Therapie | CTC monitoring | 1b | A | + |

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(andere potentielle biologische Faktoren: siehe Kapitel „Prädiktive Faktoren“)

* In klinischen Studien

Palliative Chemotherapie Ziele

Oxford LOE 1b

GR A

AGO ++

Mono-Chemotherapie:

- **Günstiger therapeutischer Index**
- **Indiziert bei**
 - **Langsamer, nicht lebensbedrohlicher Progression**
 - **Resistenz oder Progression unter endokriner Therapie**

Poly-Chemotherapie:

- **Ungünstiger therapeutischer Index**
- **Indiziert zum Erzielen einer schnellen Remission bei**
 - **Ausgeprägten Symptomen**
 - **Lebensbedrohlichen Metastasen**
- **Überlebensvorteil im Vergleich zur sequenziellen Gabe der gleichen Substanzen ist nicht bewiesen**

Der therapeutische Index berücksichtigt Effektivität, Toxizität, und Lebensqualität

Palliative Systemtherapie

LoE 1c

GR A

AGO: ++

- **Bewertung der Compliance vor und während der Therapie (insbesondere bei älteren Patientinnen, bei reduziertem AZ oder relevanten (Komorbiditäten)**
- **Regelmäßige Beurteilung subjektiver und objektiver Toxizitäten, des AZ und von Symptomen**
- **Dosierung entsprechend publizierten Protokollen**
- **Beurteilung der Tumorlast ca. alle 2 Monate, d.h. alle 2–4 Zyklen. Die Beurteilung einer Zielläsion muss adäquat sein, bei langsam progredienter Krankheit sind längere Intervalle akzeptabel.**

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Palliative Chemotherapie Dauer

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**Solange wie der therapeutische Index
positiv bleibt**

➤ Therapie bis zum besten Ansprechen

2b B +

➤ Therapie bis zur Progression

2b B +

➤ Wechsel auf alternatives Schema
vor einer Progression

2b B -

➤ Therapiestopp bei

1c A ++

➤ Progression

➤ Nicht zu beherrschender Toxizität

Chemotherapie beim mBC - Allgemeine Überlegungen: Substanzwahl

AGO: ++

Die Wahl des Zytostatikums ist abhängig von:

- **ER/PR, HER2; Kombination mit Biologicals**
- **Frühere Behandlungen (und ihre Toxizitäten)**
- **Aggressivität der Erkrankung und Lokalisation der Metastasen**
- **Biologisches Alter**
- **Begleiterkrankungen (einschließlich Organfunktionen)**
- **Erwartungen und Präferenzen der Patienten**

mBC – HER2 negativ

Palliative Chemotherapie

Erstlinienbehandlung*

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Mono-Therapie:

- Doxorubicin, Epirubicin, Mitoxantron (A),
Peg.liposomales Doxorubicin(A_{lip})
- Docetaxel (q3w), Paclitaxel (q1w) (T)
- Vinorelbin
- Capecitabin
- Nab-paclitaxel
- Ixabepilone

| | | |
|----|---|----|
| 1b | A | ++ |
| 1b | A | ++ |
| 3b | B | + |
| 2b | B | + |
| 2b | B | + |
| 1b | B | - |

Poly-Chemotherapie:

- A + T
- Paclitaxel + Capecitabin
- Docetaxel + Capecitabin nach adj. A
- T + Gemcitabin nach adj. A
- (F) + A + C oder A_{lip} + C
- CMF(1+8)
- BMF (Bendamustin)
- Ixabepilone + Capecitabin

| | | |
|-----------------|---|-----|
| 1b | A | ++ |
| 2b ^a | B | + |
| 1b | A | + |
| 2b | B | ++ |
| 1b | B | ++ |
| 2b | B | +/- |
| 1b | B | +/- |
| 1b | B | +/- |

Berücksichtigung der Vorbehandlung:

*bei ER pos. Erkrankung nur indiziert, wenn eine endokrine Therapie nicht oder nicht mehr in Frage kommt

Palliative Chemotherapie nach Anthrazyklin-Vorbehandlung*

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| | Oxford / AGO LOE / GR | | |
|---|--------------------------|---|-----|
| ➤ Docetaxel q3w | 1a | A | ++ |
| ➤ Paclitaxel q1w | 1a | A | ++ |
| ➤ Capecitabin | 2b | B | ++ |
| ➤ Nab-Paclitaxel | 2b | B | ++ |
| ➤ Peg-liposomales Doxorubicin | 2b | B | + |
| ➤ Vinorelbin | 2b | B | + |
| ➤ Docetaxel + Peg-liposomales Doxo | 1b | B | +/- |
| ➤ Etoposid / Cisplatin | 2b | B | +/- |

* unabhängig davon, ob Anthrazykline in der adjuvanten oder first line metastasierten Situation verwendet wurden

Palliative Chemotherapie nach Taxan- und Anthrazyklin- Vorbehandlung

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➤ Experimentelle Therapien in Studien

➤ Capecitabin

2b B ++

➤ Eribulin

1b B ++

➤ Vinorelbin

2b B ++

➤ (Peg)-liposomales Doxorubicin

2b B +

➤ Gemcitabin + Cisplatin / Carboplatin

2b B +/-

➤ Gemcitabin + Capecitabin

2b B +/-

➤ Gemcitabin + Vinorelbin*

1b B -

➤ Ixabepilone + Capecitabin*

1b B -

***Cave Neutropenie / Therapeutischer Index!**

Triple-negatives metastasiertes Mammakarzinom (TNBC: ER-,PR-,HER2-)

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**Oxford / AGO
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- | | | | |
|---|-----------|----------|------------|
| ➤ Chemotherapie wie bei ER pos. HER2 neg. Pat. | | | ++ |
| ➤ Experimentelle Therapien innerhalb von Studien | | | ++ |
| ➤ Platinanaloga-basierte Regime | 4 | C | +/- |
| ➤ Bevacizumab in Kombination mit Zytostatikatherapie | 2b | B | + |

Zielgerichtete Substanzen, bei anderen Entitäten zugelassen – HER2 negatives Mammakarzinom

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| | Oxford / AGO LoE / GR | | |
|--------------------------------------|--------------------------|----------|------------|
| ➤ Sorafenib | 1b | B | - |
| ➤ Sunitinib | 1b | B | - |
| ➤ Ramucirumab + Chemotherapie | 1b^a | B | -* |
| ➤ Vandetanib | 1b | B | --* |

Bevacizumab beim HER2-neg. metastasierten Mammakarzinom

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➤ 1st line in Kombination mit:

- Paclitaxel (wöchentlich)
- Capecitabine
- Anthracyklinen
- Nab-Paclitaxel
- Docetaxel (dreiwöchentlich)

| | | |
|----|---|-----|
| 1b | B | + |
| 2b | B | + |
| 2b | B | +/- |
| 2b | B | +/- |
| 1b | B | +/- |

➤ 2nd line in Kombination mit:

- Taxanen
- Capecitabine
- Gemcitabine oder Vinorelbine

| | | |
|----|---|------|
| 1b | B | +/-* |
| 1b | B | +/-* |
| 1b | B | - |

***Studienteilnahme empfohlen**

Erstlinientherapie beim HER2 pos. metastasierten Mammakarzinom

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| | | | |
|---|-----------------|---|-------|
| ➤ Docetaxel + Trastuzumab + Pertuzumab | 1b | A | ++ |
| ➤ Paclitaxel + Trastuzumab + Pertuzumab | 5 | D | + |
| ➤ T-DM 1 (Rückfall innerhalb von 6 Monaten nach Taxan und Trastuzumab) | 2b | B | + |
| ➤ 1 st -Line Chemotherapie* + Trastuzumab | 1b | B | + |
| ➤ Trastuzumab mono | 2b | B | +/- |
| ➤ Taxan + Lapatinib | 1b ^a | B | +/- |
| ➤ Trastuzumab + Aromatase Inhibitoren (ER+) | 2b | B | +/-** |
| ➤ Lapatinib + Aromatase Inhibitoren (ER+) | 2b | B | +/-** |

*Taxane; Vinorelbine; Paclitaxel/Carboplatin; Capecitabine/Docetaxel

**siehe Kapitel Endokrin +/- targeted

Zweitlinientherapie bei HER2 pos. metastasierten Mammakarzinom (Vorbehandlung mit Trastuzumab)

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|------------|
| ➤ T-DM 1 | 1b | A | ++ |
| ➤ Capecitabine + Lapatinib | 1b | B | + |
| ➤ Trastuzumab + Lapatinib (HR neg. Pat.) | 2b | B | + |
| ➤ TBP: 2nd-Line Chemotherapie + Trastuzumab | 2b | D | + |
| ➤ Taxane + Trastuzumab + Pertuzumab | 5 | D | + |
| ➤ 2nd-Line Chemotherapie* + Trastuzumab + Pertuzumab | 5 | D | +/- |
| ➤ Trastuzumab + Aromatase-Inhibitor (ER+) | 3b | B | + |
| ➤ Lapatinib + Aromatase-Inhibitor (ER+) | 3b | B | + |

*e.g. Vinorelbine; Taxane/Carboplatin; Capecitabine/Docetaxel (Toxizität!)

Further Line Therapie bei HER2 pos. metastasiertem Mammakarzinom

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Vorbehandlung mit Trastuzumab

- **T-DM 1**
- **Capecitabine + Lapatinib**
- **Trastuzumab + Lapatinib (HR neg. Pat.)**
- **Chemotherapie + Trastuzumab + („treatment beyond progression“)**
 - **Trastuzumab + Pertuzumab**
 - **Vinorelbine + Trastuzumab + Everolimus**

Daten nach Vorbehandlung mit Trastuzumab und Pertuzumab und für TBP mit Pertuzumab sind bislang nicht verfügbar.

- **Experimentelle Anti-HER2-Regime**

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1b A ++

1b B +

2b B +

2b B +

2b B +

1b B +/-

5 D +

Trastuzumab beim HER2-positiven metastasierten Mammakarzinom

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➤ Als Monotherapie

- Nach zytostatischer Vorbehandlung
- Als 1st -line Therapie

➤ Als Kombinationstherapie

- Mit Taxanen (1st -line)
- Mit Paclitaxel / Carboplatin
- Vinorelbin (1st -line)
- Capecitabin / Docetaxel
- Andere zytotoxische Substanzen
- In Kombination mit Aromataseinhibitoren

➤ Als „treatment beyond progression“

- Mit Capecitabin
- Mit Lapatinib für schwer vorbehandelte Pat.

Therapiedauer und Dosierung:

- Beginn so früh wie möglich
- Therapie bis Progression
- Wöchentlich oder 3-wöchentlich

Oxford / AGO LoE / GR

| | | |
|----|---|----|
| 1b | A | ++ |
| 2b | B | + |

| | | |
|----|---|----|
| 1b | A | ++ |
|----|---|----|

| | | |
|----|---|----|
| 1b | A | ++ |
|----|---|----|

| | | |
|----|---|----|
| 1b | B | ++ |
|----|---|----|

| | | |
|----|---|---|
| 1b | B | + |
|----|---|---|

| | | |
|----|---|---|
| 2b | A | + |
|----|---|---|

| | | |
|----|---|-----|
| 2b | B | +/- |
|----|---|-----|

| | | |
|----|---|---|
| 1b | B | + |
|----|---|---|

| | | |
|----|---|---|
| 2b | B | + |
|----|---|---|

| | | |
|----|---|----|
| 2b | B | ++ |
|----|---|----|

| | | |
|----|---|----|
| 1b | A | ++ |
|----|---|----|

| | | |
|----|---|----|
| 2b | C | ++ |
|----|---|----|

Lapatinib beim HER2-positiven metastasierten Mammakarzinom

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In Kombination mit

- Paclitaxel als 1st line
- Capecitabine als \geq 2nd line
- AI bei ER positiver Erkrankung
- Trastuzumab für schwer vorbehandelte Patientinnen
- Bei Patientinnen mit Hirnmetastasen (Radioresistenz) in Kombination mit Capecitabine

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2b B +/-

1b B +

2b B +/-

2b B +

2b B +/-

Palliative Hochdosis-Chemotherapie

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LoE / GR

➤ Hochdosischemotherapie

(Keine Therapie außerhalb
klinischer Studien!)

1a A - -

➤ Dosisdichte Therapie

(Keine Therapie außerhalb
klinischer Studien!)

1a A -

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Osteoonkologie und Knochengesundheit

Osteoonkologie und Knochengesundheit

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Bisphosphonate beim Mammakarzinom

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| | Oxford / AGO | | |
|---|--------------|---|-----|
| | LoE / GR | | |
| ➤ Hyperkalzämie | 1a | A | ++ |
| ➤ Reduktion skelettaler Komplikationen | 1a | A | ++ |
| ➤ Reduktion von Knochenschmerzen | 1a | A | ++ |
| ➤ Therapie nach ossärer Progression | 5 | D | ++ |
| ➤ In Kombination mit neoadjuvanter Chemotherapie | 2b | C | +/- |
| ➤ Prävention von Knochenmetastasen / Überlebensvorteil | | | |
| ➤ Adjuvant bei postmenopausalen Patientinnen | 1a | A | + |
| ➤ Bei fortgeschrittener Erkrankung | 2b | C | +/- |
| ➤ Prävention von MammaCa durch orale BPs | 3b | C | +/- |
| (bei Frauen unter BP-Therapie mit niedriger Knochendichte) | | | |

Denosumab beim Mammakarzinom

Oxford / AGO
LoE / GR

- | | | | |
|---|----|---|-----|
| ➤ Reduktion der Hyperkalzämie | 2a | A | ++ |
| ➤ Reduktion skelettaler Komplikationen | 1a | A | ++ |
| ➤ Reduktion von Knochenschmerzen | 1b | B | ++ |
| ➤ Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen | 1b | A | ++ |
| ➤ Therapie nach ossärer Progression | 5 | D | + |
| ➤ Progression unter Bisphosphonaten | 4 | C | +/- |

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Bisphosphonate und Denosumab für die Therapie von Knochenmetastasen

Oxford / AGO
LoE / GR

| | | | | |
|---|---|-----------|----------|-----------|
| ➤ | Clodronat p.o. 1600 mg täglich | 1a | A | ++ |
| ➤ | Clodronat i.v. 1500 mg q3w / q4w | 1a | A | ++ |
| ➤ | Pamidronat i.v. 90 mg q3w / q4w | 1a | A | ++ |
| ➤ | Ibandronat i.v. 6 mg q3w / q4w | 1a | A | ++ |
| ➤ | Ibandronat p.o. 50 mg täglich | 1a | A | ++ |
| ➤ | Zoledronat i.v. 4 mg q4w | 1a | A | ++ |
| ➤ | Denosumab 120mg s.c. q4w | 1a | A | ++ |
| ➤ | Andere Dosierungen oder Schemata, wie z.B. aus den Studien zur adjuvanten Situation oder Osteoporosetherapie | 5 | D | -- |

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Ossäre Metastasen Radionuklidtherapie

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LoE / GR**

- | | | | |
|--|-----------|----------|----------|
| ➤ Tumorprogression nach Ausschöpfung der Standardtherapie multipler / disseminierter Skelettmetastasen und resistente Knochenschmerzen | 1b | B | + |
| ➤ ¹⁸⁶ Rhenium-hydroxyethyliden-diphosphonat (z. B. ¹⁸⁶ Re-HEDP) | 2b | B | + |
| ➤ ¹⁵³ Samarium | 1b | B | + |
| ➤ ⁸⁹ Strontium (z. B. Sr ⁸⁹) | 1b | B | + |
| ➤ ²²³ Radium | 1b | C | + |

Cave: Gefahr der Myelosuppression und Panzytopenie

Knochenmetastasen in der Wirbelsäule

Operationsindikationen

Oxford LoE: 2b

GR: C

AGO: ++

- **Spinales Kompressionssyndrom**
 - **Mit progredienter neurologischer Symptomatik**
 - **Mit pathologischen Frakturen**
- **Instabilität der Wirbelkörper**
- **Läsionen in vorbestrahlten Teilen der Wirbelsäule**

Knochenmetastasen – Spinales Kompressionssyndrom / Paraplegie

**Oxford / AGO
LoE / GR**

- **Operation zur Dekompression, Reduktion der Tumormasse und Stabilisierung (< 24 h) und Bestrahlung der Wirbelsäule (RT)** **2b C ++**
- **Bestrahlung der WS (< 24 h) +/- Steroide** **3b C ++**
- **Sofortiger Therapiebeginn** **1c D ++**

Knochenmetastasen: Operationstechniken

Wirbelsäule und Extremitäten

Oxford LoE: 3b

GR: C

AGO: +

- **Marknagelung**
- **Plattenosteosynthesen**
- **Knochenersatz durch PMMA oder Titanspacer**
- **Tumorendoprothesen**
- **Vertebroplastie / Kyphoplastie**
- **Kypho-IORT* (nur in Studien)**
- **Resektion einzelner Knochenmetastasen in der oligometastatischen Situation (Sternum, Rippen, Wirbelkörper)**

***Studienteilnahme empfohlen**

Knochenmetastasen: Strahlentherapie

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Knochenmetastasen

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| ➤ Mit Frakturrisiko | 1a | B | ++ |
| ➤ Mit Funktionseinschränkung | 1a | B | ++ |
| ➤ Mit Schmerzen | 1a | B | ++ |
| einmalige RT = fraktionierte RT | 2a | B | ++ |
| ➤ Mit neuropathischem Schmerz | 1b | B | ++ |
| ➤ Asymptomatische isolierte Metastasen | 5 | D | +/- |

Nur wenige Studien mit Mammakarzinompatientinnen!

Knochenmetastasen

Schmerztherapie nach Vorbestrahlung

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Rekurrenter Knochenschmerz in vor- bestrahlten Arealen des Skeletts

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LoE / GR**

| | | | |
|-------------------------------|----|---|----|
| ➤ Einmalige RT (1 x 8 Gy) | 3b | C | ++ |
| ➤ Fraktionierte RT (6 x 4 Gy) | 3b | C | + |
| ➤ Radionuklidtherapie | 3b | C | + |

Nebenwirkungen und Toxizitäten von Bisphosphonaten (BP) und Denosumab (Db)

**Oxford
LoE**

- **Nierenfunktionsstörungen durch i.v. Amino-Bisphosphonate**
- **Kieferosteonekrose (ONJ) typisch unter i.v. BPs und Denosumab (1,3%/1,8%)**
 - **Assoziation mit parallelem Einsatz von anti-angiogenetischen Therapien**
- **Ausgeprägte Fälle mit Hypokalzämie (Dmab>BP)**
- **Akut-Phase-Reaktion (i.v. Amino-BPs und Denosumab) 10-30%**
- **Gastrointestinale Nebenwirkungen (orale BPs) 2-10%**

1b

1b

3b

1b

1b

1b

Bei adjuvanter Bisphosphonattherapie wurden außer Akut-Phase-Reaktionen keine gravierenden Nebenwirkungen gesehen

Empfehlungen für die Prävention von Kieferosteonekrosen (ONJ)

Oxford LoE: 4

GR: C

AGO: +

- Unter Bisphosphonat- bzw. Denosumabtherapie Vermeidung elektiver Zahnbehandlungen mit Manipulationen am Kieferknochen. Falls unvermeidbar wird der prophylaktische Einsatz von Antibiotika empfohlen (**LoE 2b**)
- Zahnsanierung vor einer Bisphosphonat- bzw. Denosumabtherapie, falls möglich (**LoE 2b**)
- Information der Patientinnen über ONJ-Risiko und Instruieren über Frühsymptome
- Bei hohem ONJ-Risiko, Anwendung oraler Bisphosphonate

Unter adjuvanter Bisphosphonattherapie ist das Risiko für Kieferosteonekrosen gering

Adjuvante Bisphosphonattherapie zur Verbesserung des Überlebens

Oxford / AGO
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Clodronate (oral)

Postmenopausale Patientinnen
Prämenopausale Patientinnen

1a A +
1a B +/-

Aminobisphosphonate (iv oder oral)

Postmenopausale Patientinnen
Prämenopausale Patientinnen

1a A +
1a B +/-

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Adjuvante Bisphosphonattherapie zur Verbesserung des Überlebens

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Dosierung adjuvanter Bisphosphonate zur Verbesserung des Überlebens

- **Nicht-Aminobisphosphonate:**
- **Clodronat PO 1600mg/d (Bonefos/ Clodronsäure)**
- **Clodronat PO 1040mg/d (Ostac)**
- **Aminobisphosphonate:**
- **Zoledronat IV 4mg/6m (Zometa/ Zoledronsäure)**
- **Ibandronat PO 50mg/d (Bondronat/ Ibandronsäure)**
- **Pamidronat PO (in oraler Form in D nicht verfügbar)**
- **Risedronat PO 35mg/w (Actonel/ Risedronsäure)**
- **Alendronat PO 70mg/w (Fosamax/ Alendronsäure)**

Zu den Aminobisphosphonaten gehören:

Zoledronsäure (65%), Orales Ibandronat (24%), Orales Pamidronat (8%),
Orales Residronat (2%), Orales Alendronat (1%) (Daten aus der EBCTCG-Metaanalyse)

Therapie und Prävention des Tumorthherapie induzierten Knochenmasseverlusts / Osteoporose

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➤ Bisphosphonate

- Therapie
- Prävention

**Oxford / AGO
LoE / GR**

1b B ++
1b A +

RANK-Ligand Antikörper

- Therapie
- Prävention

1b B ++
1b A +

➤ HRT (unabhängig vom HR-Status des Tumors)

5 D -

➤ Regelmäßige Bestimmung der Knochendichte (Messintervalle entsprechend T-Wert)

2b B +

Therapie und Prävention des Tumorthherapie induzierten Knochenmasseverlusts / Osteoporose

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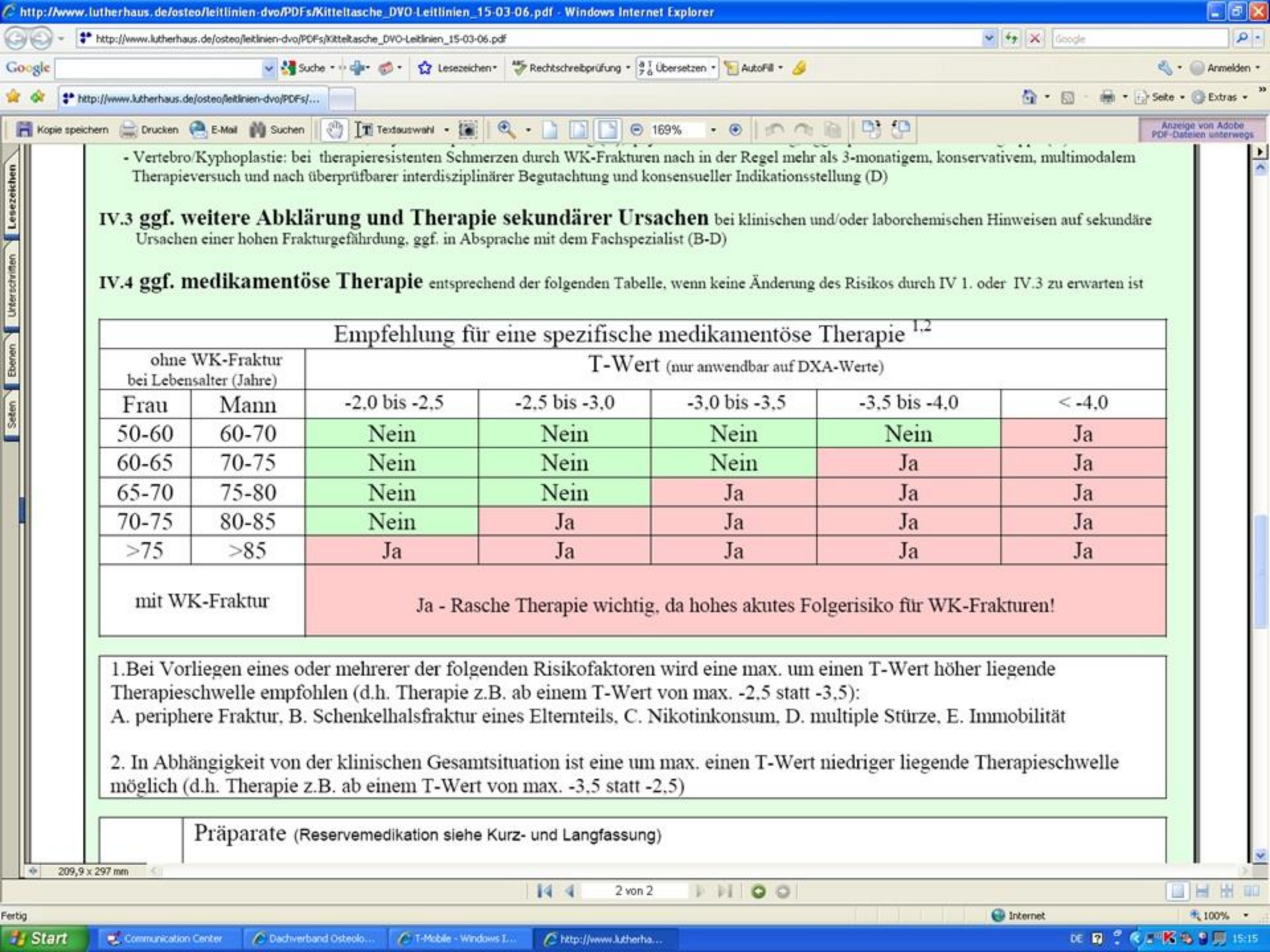
Weitere Empfehlungen (in Analogie zur DVO-Leitlinie zur Prophylaxe, Diagnostik und Therapie der Osteoporose)*

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|----|
| ➤ Sportl. / körperl. Aktivität | 4 | C | ++ |
| ➤ Vermeidung von Immobilisation | 4 | C | ++ |
| ➤ Kalzium (1000–1.500 mg/d)** | 4 | C | ++ |
| ➤ Vit. D (800–2000 U/d) | 4 | C | ++ |
| ➤ Reduktion Nikotinabusus | 4 | C | ++ |
| ➤ Vermeidung eines BMI < 20 kg/m ² | 3b | C | ++ |
| ➤ Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage) | | | |

Medikamentöse Therapie der Osteoporose

Oxford / AGO
LoE / GR

| | | | |
|---------------------------------|----|---|----|
| ➤ Alendronat 70 mg po/w* | 1b | B | ++ |
| ➤ Denosumab 60 mg sc/6m* | 1b | B | ++ |
| ➤ Ibandronat 150 mg po/m* | 1b | B | ++ |
| ➤ Ibandronat 3 mg iv/3 m | 1b | B | + |
| ➤ PTH (1-84) 100 µg sc/d | 1b | B | + |
| ➤ Raloxifen 60 mg po/d | 1b | B | + |
| ➤ Risedronat 35 mg po/w* | 1b | B | ++ |
| ➤ Strontiumranelat 2 g po/d | 1b | B | + |
| ➤ Teriparatid (1-34) 20 µg sc/d | 1b | B | + |
| ➤ Zoledronat 5 mg iv/12 m* | 1b | B | ++ |



- Vertebro/Kyphoplastie: bei therapieresistenten Schmerzen durch WK-Frakturen nach in der Regel mehr als 3-monatigem, konservativem, multimodalem Therapieversuch und nach überprüfbarer interdisziplinärer Begutachtung und konsensueller Indikationsstellung (D)

IV.3 ggf. weitere Abklärung und Therapie sekundärer Ursachen bei klinischen und/oder laborchemischen Hinweisen auf sekundäre Ursachen einer hohen Frakturgefährdung, ggf. in Absprache mit dem Fachspezialist (B-D)

IV.4 ggf. medikamentöse Therapie entsprechend der folgenden Tabelle, wenn keine Änderung des Risikos durch IV 1. oder IV.3 zu erwarten ist

Empfehlung für eine spezifische medikamentöse Therapie^{1,2}

| ohne WK-Fraktur bei Lebensalter (Jahre) | | T-Wert (nur anwendbar auf DXA-Werte) | | | | |
|--|-------|---|---------------|---------------|---------------|--------|
| Frau | Mann | -2,0 bis -2,5 | -2,5 bis -3,0 | -3,0 bis -3,5 | -3,5 bis -4,0 | < -4,0 |
| 50-60 | 60-70 | Nein | Nein | Nein | Nein | Ja |
| 60-65 | 70-75 | Nein | Nein | Nein | Ja | Ja |
| 65-70 | 75-80 | Nein | Nein | Ja | Ja | Ja |
| 70-75 | 80-85 | Nein | Ja | Ja | Ja | Ja |
| >75 | >85 | Ja | Ja | Ja | Ja | Ja |
| mit WK-Fraktur | | Ja - Rasche Therapie wichtig, da hohes akutes Folgerisiko für WK-Frakturen! | | | | |

1. Bei Vorliegen eines oder mehrerer der folgenden Risikofaktoren wird eine max. um einen T-Wert höher liegende Therapieschwelle empfohlen (d.h. Therapie z.B. ab einem T-Wert von max. -2,5 statt -3,5):

A. periphere Fraktur, B. Schenkelhalsfraktur eines Elternteils, C. Nikotinkonsum, D. multiple Stürze, E. Immobilität

2. In Abhängigkeit von der klinischen Gesamtsituation ist eine um max. einen T-Wert niedriger liegende Therapieschwelle möglich (d.h. Therapie z.B. ab einem T-Wert von max. -3,5 statt -2,5)

Präparate (Reservemedikation siehe Kurz- und Langfassung)

Therapieempfehlung für Personen ohne spezifische Risiken und/oder Frakturen

Schwellenwerte der T-Werte der Knochendichte für eine medikamentöse Therapie in Abhängigkeit vom Geschlecht und dem Lebensalter für Personen ohne prävalente Frakturen oder andere spezifische Frakturrisiken

Lebensalter in Jahren T-Wert

| Frau | Mann | T-Wert |
|-------|-------|--------|
| <50 | <60 | −4,0 |
| 50–60 | 60–70 | −4,0 |
| 60–65 | 70–75 | −3,5 |
| 65–70 | 75–80 | −3,0 |
| 70–75 | 80–85 | −2,5 |
| >75 | >85 | −2,0 |

Therapieempfehlung für Personen mit spezifische Risiken und/oder Frakturen

Risikofaktoren, die die Therapieschwelle mitbestimmen (auszugsweise*)

1. Allgemeine Risiken

| | |
|--|---|
| periphere Fraktur nach dem 50. Lebensjahr | B |
| multiple Stürze | B |
| Immobilität | B |
| fortgesetzter Nikotinkonsum | B |
| Abnahme der DXA-Knochendichte am Gesamtfemur um 5% und mehr in 2 Jahren | B |
| Hypogonadismus | B |

2. Krankheiten

| | |
|-------------------------|---|
| Diabetes mellitus Typ 1 | B |
| rheumatoide Arthritis | D |

3. Medikamente

| | |
|--|---|
| Antiandrogene/ Antiöstrogene Therapie | B |
| Aromatasehemmer-Therapie | D |
| orale Glukokortikoide < 7,5 mg für mehr als 3 Monate | B |

*http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2009

Neue DVO-Leitlinie erscheint vermutlich 2014

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Besondere Situationen und Lokalisationen in der metastasierten Situation

Besondere Situationen und Lokalisationen in der metastasierten Situation

- **Version 2002:**
Dall / Fersis / Friedrich
- **Versionen 2003–2013:**
Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon
- **Version 2014:**
Fehm / Gerber

Besondere Metastasenlokalisationen

- **Leber und Lunge**
- **Maligne Pleura- und Perikardergüsse**
- **Aszites**
- **Knochenmarkinfiltration**
- **Weichteilmetastasen**
- **Alle anderen Organe sind mögliche Lokalisationen (Augen, Haut, Nebennieren, Ovarien, Uterus, Magen, Darm, ...)**
- **Siehe auch Kapitel zur ZNS-Metastasen / Lokoregionäres Rezidiv (Lokoregionäres Rezidiv Behandlungsoptionen bei nicht kurativen Fällen)**

Allgemeine Aspekte der Metastasen Chirurgie

Oxford / AGO LoE / GR

| | | | |
|---|-----------|----------|------------|
| ➤ Histologischer / zytologischer Nachweis der Metastasierung | 3 | B | + |
| ➤ Systemische Therapie bevorzugt | 2a | B | ++* |
| ➤ Operative Therapie bei gutem Therapieansprechen der systemischen Therapie | 2b | C | + |
| ➤ Option bei Patienten in gutem Zustand mit spät aufgetretenen Oligometastasen | 3 | D | + |
| ➤ Indikation zur lokalen Behandlung bei Schmerzen, Exulzeration, Ileus persistierende Metastase(n) nach Abschluss der Systemtherapie | 5 | D | +/- |
| ➤ Systemischen Behandlung nach Chirurgie | 5 | D | ++ |

* Siehe auch Kapitel zur Systemtherapie in der metastasierten Situation

Mammachirurgie in der primär metastasierten Situation

Oxford / AGO

LoE / GR

- Lokale Therapie (R0) des Primärtumors*
- Axillaoperation bei cN1
- Sentinel in cN0

2b C +/-

5 C +/-

5 C -

* insbesondere bei Knochenmetastasen

Hepatische Metastasen

Lokale Therapie

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LoE / GR

- **Chirurgische Resektion (R0)**
Individuelle Fälle (Leberfunktion) mit resektablen Metastasen
HR positiv; Chemotherapie sensibel
- **Regionale Chemotherapie**
- **Regionale Radiotherapie**
(SIRT, Radiochemoembolisation, andere Bestrahlungsverfahren)
- **Thermoablation**
(RFA, LITT, Kryotherapie)

3b C +/-

4 C +/-

3b C +/-

4 C +/-

3b C +/-

Pulmonale Metastasen

Lokale Therapie

Oxford / AGO

LoE / GR

**VATS oder konventionelle
chirurgische Resektion (R0)**

3b C +/-

**Thermoablation CT-gesteuerte RFA,
LITT, Kryotherapie**

3b C +/-

VATS = video-assistierte Thoraxchirurgie

Maligner Pleuraerguss (MPE)

Inzidenz:

- ~ 10 % aller Mammakarzinompatientinnen
- ~ 50 % der metastasierten Patientinnen
- ~ 30 % aller MPE sind durch MaCa verursacht

Symptomatik:

- Extensive MPE haben meistens eine maligne Ursache
- Die Mehrheit der MPE sind symptomatisch
- Das Überleben ist assoziiert mit weiteren Metastasenlokalisationen, Alter und Ausdehnung der Pleura-Meta.

Diagnostik:

- Klinische Untersuchung
- Röntgen, Ultraschall, CT
- Histologischer / Zytologischer Nachweis durch Punktion oder Thorakoskopie

Maligner Pleuraerguss

Lokale Therapie

Oxford / AGO
LoE / GR

| | 1b | B | ++ |
|---|----|---|-----|
| ➤ VATS und Talkum-Pleurodese* | | | |
| ➤ Medikamentöse Pleurodese | | | |
| ➤ Talkum | 1a | B | ++ |
| ➤ Bleomycin, Doxycyclin, Mitoxantron | 2b | C | +/- |
| ➤ Povidon-Jodid (in Deutschland nicht zugelassen) | 3b | C | +/- |
| ➤ Kontinuierliche Pleuradrainage | 2a | B | + |
| ➤ Systemtherapie nach Pleurodese | 3b | C | +/- |
| ➤ Lokale Antikörpertherapie (z.B. Catumaxomab) | 3b | C | - |
| ➤ Wiederholte Pleurapunktionen | 5 | D | - |

* Adäquate Schmerztherapie

VATS = video-assisted thorac. surgery

Maligner Aszites

Lokale Therapie

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Behandlung in Abhängigkeit von:

- Symptomen**
- Klinischen Manifestationen**
- Ansprechen auf Systemtherapie**

Aszites:

- **Punktion, Drainage**
- **Lokale Chemotherapie**
- **Systemische Therapie**
- **Lokale Antikörpertherapie (z.B. Catumaxomab)**

Oxford / AGO
LoE / GR

| | | |
|-----------|----------|------------|
| 4 | D | ++ |
| 3b | D | +/- |
| 3b | D | ++ |
| 3b | D | +/- |

Maligner Perikarderguss

Lokale Therapie

**Oxford / AGO
LoE / GR**

Symptomatischer Perikarderguss:

- | | | | |
|---|-----------|----------|------------|
| ➤ Drainage, chirurgische Fensterung des Perikards | 3b | B | ++ |
| ➤ Thorakoskopie (VATS) | 4 | D | + |
| ➤ Ultraschall geführte Punktion und Instillation von Mitoxantron, Cisplatin | 4 | D | +/- |

Knochenmarkinfiltration (mit Panzytopenie)

**Oxford / AGO
LoE / GR**

Wöchentliche Chemotherapie*:

**Epirubicin, Doxorubicin, Paclitaxel
Capecitabine**

4 D ++

HER2 pos.: plus anti-HER2 Therapie

5 D ++

*** Beachte Vorbehandlung**

Weichteilmetastasen

Lokale Therapie

Oxford / AGO

LoE / GR

**Bestrahlung, falls keine Op-Indikation
oder aber nach Operation**

- | | | |
|--|-------------|-----------|
| ➤ Parese, Rückenmarkskompression* | 2b C | ++ |
| ➤ Plexusinfiltration | 3b C | ++ |
| ➤ Weichteilmetastasen | 3b C | + |

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ZNS-Metastasen beim Mammakarzinom



ZNS-Metastasen beim Mammakarzinom

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- **Versionen 2003–2013:**
**Bischoff / Diel / Friedrich / Gerber / Lück
/ Maass / Nitz / Jackisch / Jonat /
Junkermann / Rody / Schütz**

- **Version 2014:**
Maass / Müller

ZNS-Metastasen beim Mammakarzinom – Inzidenz

- **Das Mammakarzinom ist zweithäufigste Ursache von ZNS-Metastasen**
- **In Autopsie-Kollektiven:**
 - **Parenchymale ZNS Metastasen:** ~30 - 40 %
 - **Leptomeningeale ZNS-Metastasen:** 5 - 16 %
- **Stetig steigende Inzidenz (10 % ➔ 40 %)**
- **Anstieg der Inzidenz verursacht durch:**
 - **Effektivere Behandlungsoptionen der extrazerebralen Metastasen**
 - **Vermehrter Einsatz der MR-Diagnostik**
- **Datenlage für Behandlung von ZNS-Metastasen des Mammakarzinoms ist unbefriedigend, da Studien meist nicht Mammakarzinom-spezifisch. Teilnahme an der deutschen Registerstudie zu ZNS-Metastasen Mammakarzinom empfohlen.**

ZNS-Metastasen beim Mammakarzinom – Risikofaktoren

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➤ Primärtumor:

- **Negativer Östrogenrezeptor-Status (Basalzell-Typ / triple negativ)**
 - **Hohes Grading, hohes Ki-67**
 - **HER2 und / oder EGFR (HER1) Überexpression**
- ## ➤ Vorbehandlung mit Trastuzumab in der metastasierten Situation

ZNS-Metastasen sind häufiger Östrogenrezeptor-neg. und überexprimieren häufiger HER2 und / oder EGFR

Keine Evidenz für Hirnmetastasen-Screening bei asymptomatischen Patientinnen

Graded Prognostic Assessment (GPA)

Arbeitsblatt zur Abschätzung des Mortalitätsrisikos bei Hirnmetastasen (BM)

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| | 0 | 0.5 | 1 | 1.5 | 2 | Score |
|-------------------|-------|------|-------|--------|------|-------|
| Prognostic Factor | | | | | | |
| KPS | 50 | 60 | 70-80 | 90-100 | n/a | _____ |
| Subtype | Basal | n/a | LumA | HER2 | LumB | _____ |
| Age, years | > 60 | < 60 | n/a | n/a | n/a | _____ |
| Sum total | | | | | | _____ |

Median survival by GPA:

GPA 0-1.0 = 3.4 months

GPA 1.5-2.0 = 7.7 months

GPA 2.5-3.0 = 15.1 months

GPA 3.5-4.0 = 25.3 months

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive;
HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases;
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky
performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

Unabhängige Prognosefaktoren bei Hirnmetastasen eines Mammakarzinoms

Multivariate analyses of significant factors associated with survival after WBRT

- OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %
- Median survival time by Recursive partitioning analysis (RPA) class in months: Class I: 11.7, class II: 6.2 and class III: 3.0

| VARIABLE | P | HR | (95%-confidence interval) | |
|-------------------------|---------|------|---------------------------|------|
| SURGICAL RES | <0.0001 | 4.34 | 2.5 | 7.14 |
| SINGLE METASTASES | 0.14 | 1.08 | 0.97 | 1.21 |
| KPS \geq 70 | 0.55 | 1.31 | 0.55 | 3.23 |
| BRAIN MET SCORE (BS-BM) | 0.58 | 0.63 | 0.12 | 3.29 |
| RPA | <0.0001 | 1.64 | 1.32 | 2.04 |
| CONTR PRIM TU | 0.66 | 0.92 | 0.63 | 1.34 |
| NO EXCRANIAL MET | <0.0001 | 2.38 | 1.63 | 3.44 |

Hirnmetastasen (1–3 Läsionen)

Oxford / AGO

LoE / GR

WBRT + SRS Boost oder Neurochirurgie (vs. WBRT) **2a** **B** **++**
Verbessert lokale Kontrolle, aber nicht Überleben

SRS (<~3 cm) oder Neurochirurgie +/- WBRT* **2b** **B** **++**

WBRT** **2b** **B** **+**

Stereotactic fractionated RT (SFRT) **3b** **B** **+/-**

* In Einzelfällen kann auf die zusätzliche WBRT verzichtet werden. Zusätzliche WBRT erhöht die lokale Kontrolle und Symptomkontrolle, nicht aber das Überleben in allen Kohorten. Eine kombinierte Behandlung wird vor allem bei Patientinnen mit singulären Metastasen und gutem Allgemeinzustand empfohlen.

** Bei Patientinnen mit ungünstiger Prognose und / oder Allgemeinzustand

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy

Mögliche Entscheidungsfaktoren Neurochirurgie versus Stereotaktische Radiochirurgie

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Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
need for immediate decompression, life-threatening symptoms
- Tumor size > ~ 3cm not allowing stereotactic radiosurgery
- Surgically favorable location

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery

Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation after surgical resection or radiosurgery

| | after surgical resection (n=160) | | after radiosurgery (n=199) | |
|------------------|-------------------------------------|------------------|-------------------------------|------------------|
| | WBRT | observation | WBRT | observation |
| Local recurrence | 27% | 59% (p<0.001) | 19% | 31% (p=0.040) |
| New lesions | 23% | 42% (p=0.008) | 33% | 48% (p=0.023) |

- Only 12% of the patients had brain metastases from breast cancer.
- Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).
- Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.

Multiple Hirnmetastasen

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- **WBRT (supportiv Steroide*)**
 - **Prolongierte RT (≥ 1 Woche)**
- **Radiochemotherapie**
- **Chemotherapie allein**
- **Corticosteroide allein**

| | | |
|----|---|-----|
| 1a | A | ++ |
| 3b | B | ++ |
| 3b | C | +/- |
| 3a | D | +/- |
| 3a | B | +/- |

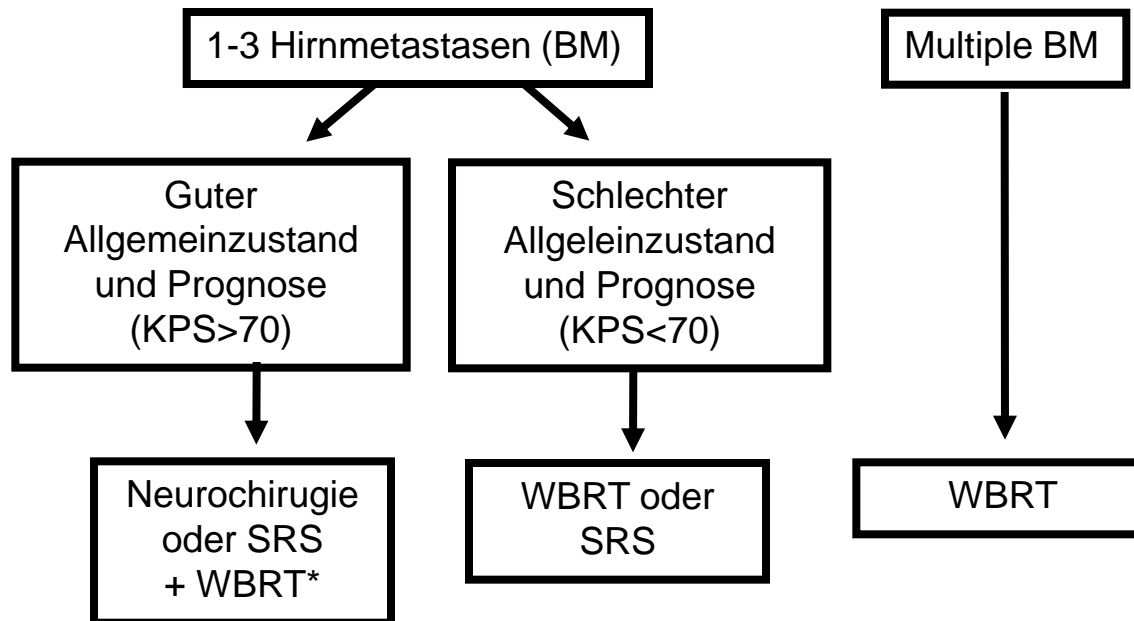
Bei Radioresistenz / Rezidiv:

- **Chemotherapie allein**
- **Lapatinib +/- Capecitabin (HER2-pos. Fälle)**
- **Erneute Strahlentherapie (falls möglich)**

| | | |
|----|---|-----|
| 3a | D | +/- |
| 2b | B | + |
| 3a | D | +/- |

***symptomadaptiert**

Mögliche Behandlungsstrategie für Hirnmetastasen eines Mammakarzinoms



* In Einzelfällen kann auf die zusätzliche WBRT verzichtet werden. Zusätzliche WBRT erhöht die lokale Kontrolle und Symptomkontrolle, nicht aber das Überleben in allen Kohorten. Ein aggressiverer Behandlungsansatz wird vor allem bei Patientinnen mit gutem Allgemeinzustand, singulären Metastasen und guter Prognose empfohlen.

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy

Systemische und symptomatische Therapie von Hirnmetastasen

Oxford / AGO
LoE / GR

- | | | | |
|--|----|---|-----|
| ➤ Fortsetzung der anti-HER2-Therapie im Falle einer extrakranialen Remission | 2c | C | + |
| ➤ Lapatinib + Capecitabin als initiale Behandlung (HER2 positiv) | 1b | B | +/- |
| ➤ Chemotherapie als alleinige Primärbehandlung | 3 | D | - |
| ➤ Routinemäßiger Einsatz von Antikonvulsiva | 3 | C | - |
| ➤ Glucocorticoide (nur wenn Symptome und / oder Verdrängungseffekt) | 3 | C | ++ |

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LANDSCAPE: An FNCLCC Phase II Study with Lapatinib (L) and Capetitabine (C) in Patients with Brain Metastases (BM) from HER2-positive (+) Metastatic Breast Cancer (MBC) before Whole-brain Radiotherapy (WBRT)

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| | |
|--------------------------|---------|
| Nr. of eligible patients | N=45 |
| CNS- ORR | 67% |
| Median TTP | 5.5 Mo. |
| Median time to WBRT | 8.3 Mo. |

Leptomeningeosis carcinomatosa

Lokale Therapie

Oxford / AGO
LoE / GR

Intrathekale oder intraventrikuläre Therapie

➤ MTX 10-15 mg 2-3x/ Woche (+/- Folsäure-Rescue)

2b B ++

➤ Liposomales Cytarabin 50 mg, q 2w

3b C ++

➤ Thiothepa

3b C +

➤ Steroide

4 D +/-

➤ Trastuzumab

4 C +/-

Radiotherapie

➤ Fokal (bei größerem Tumervolumen)

4 D +

➤ WBRT

4 D +

➤ Neuroaxe (disseminierte spinale Herde)

4 D +/-

Aufgrund der schlechten Prognose einer Leptomeningeosis carcinomatosa sollte auch rein symptomatische Therapie erwogen werden, insbesondere bei Patientinnen mit schlechtem Allgemeinzustand

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Komplementäre Therapie

„Survivorship“

Komplementäre Therapien

Hormontherapie

„Survivorship“ (Rezidiv-Prävention)

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Thomssen**
- **Version 2014:**
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„Alternative“ Therapien

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„Integrative Onkologie“

CAM

Komplementäre + Alternative Medizin

Komplementär

*in Ergänzung zur
wissenschaftlich
begründeten
Medizin*

Alternativ

*anstelle der
wissenschaftlich
begründeten
Medizin*

„Unkonventionelle Methoden“

UCT

**Unkonventionelle
Therapien**

Unkonventionell

*unbewiesene
Außenseiter-
Methoden*

Komplementäre Therapien prä- und postoperativ

Oxford
LoE / GR

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Präoperativ:

- Hypnose (reduziert Ängste, Schmerz, Übelkeit, Fatigue)

1b B +/-

Postoperativ:

- Akupunktur (zur Schmerzlinderung)
- Akupunktur (bei Übelkeit, Erbrechen)
- Frühzeitige Bewegungstherapie postop.
beugt Dysfunktion der oberen Extremität vor
CAVE: vermehrt Wundsekret
- Prophylaktische Lymphdrainage

2b B +/-

2b B +

1a A +

1b B -

Komplementäre Therapien

Behandlungsphase - Einfluss auf Toxizität II

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| | Oxford LoE / GR | AGO |
|--|--------------------|-------|
| ➤ Antioxidanzien (Suppl.) | 1b B | - |
| ➤ Hochdosiert Vitamin C | 1b C | - |
| ➤ Vitamin E | 2b D | - |
| ➤ Selen zur Linderung von Nebenwirkungen | 1b B | - |
| ➤ Co-Enzym Q 10 (Fatigue, Lebensqualität) | 1b B | - |
| ➤ Proteolytische Enzyme (gegen Chemotherapie-induzierte Toxizität) | 3b B | - |
| ➤ Verbesserung der Wundheilung durch Chinesische Kräutermedizin | 1b B | -*inf |
| ➤ Sauerstoff- und Ozon-Therapie | 5 D | - - |

* Infusion in Dtl. nicht geprüfter Substanzen

Komplementäre Therapien unter Chemotherapie Behandlung von Nebenwirkungen

Oxford AGO
LoE / GR

➤ Chinesische Kräutermmedizin

1b B -

zur Behandlung chemotherapiebedingter Nebenwirkungen

kann in Hinblick auf Verbesserung v. Knochenmarkfunktion u. Lebensqualität günstig sein

➤ Homöopathische Medizin

1b B +/-

gegen therapiebedingte Nebenwirkungen

- Topische Calendula (>=20% Calendulaanteil) zur Prophylaxe einer akuten Dermatitis unter Strahlentherapie
- Traumeel S Mundspülung bei chemotherapieinduzierter Stomatitis

➤ Topische Anwendung Silymarin (Mariendisteleextrakt)

3a B +/-

➤ Akupunktur zur Verbesserung von:

- Chemotherapie-induzierte Übelkeit, Erbrechen
- Aromatasehemmer-induzierte Arthralgie
- Kognitive Dysfunktion
- Fatigue
- Schmerzen
- Leukopenie

1a B +
2b C +
5 D +/-
1a B +
1a B +/-
2b B -

Komplementäre Therapien

Behandlungsphase - Mind-Body Medizin I

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MBSR (Mindfulness-Based Stress Reduction –
dt. Achtsamkeits-basierte Stressbewältigung)
Programm verbessert Lebensqualität, Bewältigungs-
strategien, Achtsamkeit, vermindert
Stress und Depression

1b A +

Körperliches Training / Sport

mind. 150 Min. moderates Ausdauertraining pro Woche
in Kombination mit kräftigendes Gerätetraining (2x p/Wo.)
verbessern Lebensqualität, kardiorespiratorische Fitness ,
körperliche Leitungsfähigkeit und Fatigue

1a A ++

Komplementäre Therapien

Behandlungsphase - Mind-Body Medizin II

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LoE / GR

Yoga

Verbesserung von Lebensqualität, Stress, Angst und Depression

Verbesserung von Fatigue

1b A +

2a B +/-

Qigong

Hinweise auf Verbesserung von Lebensqualität, Fatigue, Stimmung

2a B +/-

Tai-Chi

Verbesserung von Lebensqualität, Muskelstärke,

2b D +/-

Hypnose (in Kombination mit kognitiver Therapie)

Verbesserung von Fatigue und Muskelanspannung unter Radiotherapie

2a B +/-

Komplementäre Therapien

Rezidiv-Prävention I

Beeinflussbare Lebensstilfaktoren – Sport - Genussmittel

Oxford / AGO

LoE / GR

➤ **Körperliches Training / Sport**

1a A ++

(das Äquivalent zu 3-5 Std.
mäßiggradigem „Walking“ verbessert
DFS und OS und kardiopulmonale Funktion)

➤ **Nikotinabusus**

1b A -

➤ **Alkohol (>6 g/die)**

1b A -

Komplementäre Therapien

Rezidiv Prävention II

Beeinflussbare Lebensstilfaktoren - Ernährung

Oxford AGO
LoE / GR

- | | | | |
|---|-------------------------|----------|------------|
| ➤ Anstreben eines normalen BMI/ Abnehmen bei Übergewicht (verbessert Prognose – DFS/OS) | 2b | B | ++ |
| ➤ Beachten genereller Ernährungsempfehlungen (z.B. von DGE, WCRF) | 2a | B | + |
| ➤ Ernährung mit geringem Fettanteil (verbessert Prognose – DFS – v. a. postmenopausal, ER neg.; ≤20% Fettkalorien, nur mit Ernährungsberatung!) | 1b⁽⁻⁾ | B | + |
| ➤ Lignan-/Ballaststoff-haltige Lebensmittel (u.a. Saaten z.B. Leinsamen) | 2a | B | +/- |
| ➤ Diät-Extreme (are associated with less favourable outcomes) | 1b | B | -- |

Komplementäre Therapien

Rezidiv-Prävention III

Pflanzliche Therapieansätze - Nahrungsergänzung

Bei laufender onkologischer Standardtherapie: Cave: Medikamenten-Interaktionen!

Oxford
LoE / GR

AGO

| | | | |
|--|----|---|----------|
| ➤ Komplement./alternative Therapien statt Systemtherapie | 2b | B | -- |
| ➤ Antioxidanzien (nach Abschluss Radiatio) | 2b | B | +/- |
| ➤ Orthomolekulare Substanzen (Selen, Zink...) | 5 | D | - |
| ➤ Vitamine (zusätzlich zu ausgewogener Ernährung) | 2b | B | - |
| ➤ Proteolytische Enzyme (Papain, Trypsin, Chymotrypsin) | 3b | B | - |
| ➤ Sojaprodukte (Phytoöstrogene) Bei rezeptorpositivem Tumor | 2b | B | +/- - |
| ➤ Traubensilberkerze (Cimicifuga racemosa) | 2b | C | +/- |
| ➤ Mistellektine (Viscum album) | 1b | C | - |
| ➤ Thymuspeptide (Einfluss auf Überleben) | 2a | B | - |
| ➤ Sauerstoff- und Ozon-Therapie | 5 | D | -- |
| ➤ Antioxidative Supplemente nach Beendigung der Radiotherapie | 2b | B | +/- |
| ➤ Laetrile (Aprikosenkernextrakt) | 1c | D | -- |
| ➤ Cancer bush (Sutherlandia frutescens), Devil's claw (Harpagophytum procumbens), Rooibos Tee (Aspalathus linearis), Bambara-Erdnuss (Vigna subterranean) | 5 | D | - |

Komplementäre Therapien

Postmenopausale Symptome I

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Allgemeine Ansätze:

- | | | | |
|---|-----------|----------|----------|
| ➤ Körperliches Training / Sport | 2b | D | + |
| ➤ Mind Body-Medizin (Yoga, Hypnose, Schulung, Beratung) | 1b | B | + |
| ➤ Akupunktur (Cave: keine Nadeln in Tumorareale einbringen: Gefahr der Zellverschleppung mit Hautfiliae) | 1a | A | + |

Komplementäre Therapien

Postmenopausale Symptome II

Pflanzliche Therapieansätze

Bei laufender onkologischer Standardtherapie: **CAVE Medikamenten-Interaktionen!**

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| | | | |
|--|----|---|-----|
| ➤ Aus Soja abgeleitete Phytoöstrogene - Isoflavonoide (Aktivierung von MaCa-Zellen insbes. bei hormon- rezeptorpositiver Erkrankung nicht ausgeschlossen) | 1b | A | - |
| ➤ Leinsamen (40g/d) (bei HR+ ≤ 10g/d (1 Essl.)) | 2b | B | +/- |
| ➤ Traubensilberkerze* gegen Hitzewallungen (Effektivität gegen Hitzewallungen nicht bewiesen) | 1b | A | +/- |
| ➤ Johanniskraut-Produkte in Kombinationstherapie** (pharmakologische Interferenz mit endokriner Therapie, Zytostatika und Tyrosinkinase-Inhibitoren) | 1b | A | -- |
| ➤ Kava-Kava (Piper methysticum) | 5 | D | -- |
| ➤ Rotklee-Blätter (Trifolium pratense) | 5 | D | -- |
| ➤ Dong Quai Wurzel (Angelica sinensis) | 5 | D | -- |
| ➤ Ginseng Wurzel (Panax ginseng or P. quinquefolius) | 5 | D | - |
| ➤ Bromelain + Papain + Selen + Lektin (bei AI-induzierten Gelenkbeschwerden) | 3b | B | +/- |
| *Remifemin® / **Remifemin-Plus® | | | |

Komplementäre Therapien

Verminderung von Karzinomschmerzen

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LoE / GR

- | | | | |
|--|----|---|-----|
| ➤ Akupunktur bei Karzinomschmerzen | 2b | D | +/- |
| ➤ Transkutane elektrische Nervenstimulation (TENS) bei Karzinomschmerzen | 2b | D | +/- |

CAVE: Keine Verzögerung der Diagnostik!

Immundiagnostik und Immuntherapien

Immundiagnostik:

- **Bestimmung von:**
 - Immunologischen Parametern im peripheren Blut

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5 D -

Lokale Immuntherapien:

- Imiquimod topisch bei Hautmetastasen

4 C +/-

Systemische Immuntherapien (einschließlich u.g. Therapien) nur in kontrollierten klinischen Studien

++

- HER2-Vakzinierung in Hochrisikokollektiven 3b C +/-
- Immunomodulation (z.B. Zugabe von Nov-2 zur Chemo AC –T) 5 D +/-
- Intradermale Vakzinierung von Dendritischen Zellen 4 C +/-
- Aktive Vakzinierungen 5 D -
- Passive Vakzinierungen 2b C -
- Therapie mit Onkoviren 4 C -
- Zytokine 3 c -



Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Options for Primary Prevention: Modifiable Lifestyle Factors

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- **Version 2012:**
Dall / Diel
- **Version 2013:**
Maass / Mundhenke
- **Version 2014:**
Scharl / Stickeler

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Risk Factors for Breast Cancer

Non-modifiable risk factors

- **Older age**
- **Genetic risk factors**
- **Family cancer history**
- **Personal history of breast lesions**
 - **Non-proliferative lesions**
 - **Proliferative lesions w/o atypia**
 - **High risk lesions (ADH, LIN)**
 - **Breast cancer (DCIS, InvBC)**
- **Breast density**
- **Chest irradiation**
- **Lifetime number of menstrual cycles**
 - **Early menarche, late menopause, mat. pregnancy factors (e.g. preeclampsia (risk reduction), gestational diabetes and low phys. activity (risk increase))**

Reproductive risk factors

- **Lower number of births or no pregnancy**
- **Higher age at first full term delivery**

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Modifiable risk factors

- **Less breast feeding**
- **BMI <18.5 and > 25 and especially > 40 (obesity)**
- **Diabetes mellitus Type II**
- **Food content, vitamin D deficiency**
- **Steroid hormone therapy**
 - Recent oral contraceptive use
 - Hormone therapy in postmenopausal women
- **Alcohol intake**
- **Smoking**
- **Light exposure at night (night shifts)**
- **Less physical activity**
- **Toxic agents in fetal and early childhood development (DES, polyfluoroalkyls)**

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The Expert Report »

Historical Overview

Business Plan

The People Behind the Report

Recommendations

The Policy Report »

**Communicating
the Reports »**

Resource Centre »

The Scientific Process »

**Continuous Update
Project »**

Our Global Network »

Contact Us

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[Home](#) » [About the Report](#) » [Recommendations](#)

Recommendations

The Second Expert Report, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, features eight general and two special recommendations. The 10 recommendations are listed below. Together they comprise a blueprint that people can follow to help reduce their risk of developing cancer.

Click on each recommendation to find out more about it.

CHAPTER 12 of the Report features the recommendations in detail as does the Report **summary**.

BODY FATNESS

Be as lean as possible within the normal range of body weight

PHYSICAL ACTIVITY

Be physically active as part of everyday life

FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN

Limit consumption of energy-dense foods

Avoid sugary drinks

PLANT FOODS

Eat mostly foods of plant origin

ANIMAL FOODS

Limit intake of red meat and avoid processed meat

ALCOHOLIC DRINKS

Limit alcoholic drinks

PRESERVATION, PROCESSING, PREPARATION

Limit consumption of salt

Avoid mouldy cereals (grains) or pulses (legumes)

DIETARY SUPPLEMENTS

Aim to meet nutritional needs through diet alone

BREASTFEEDING (Special Recommendation)

Mothers to breastfeed; children to be breastfed

CANCER SURVIVORS (Special Recommendation)

Follow the recommendations for cancer prevention

The policy implications of the recommendations are explored in the **Policy Report**.

Prevention by Changing Pregnancy Related Factors

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LoE / GR**

- **Any full term pregnancy**
- **Number of pregnancies**
- **First full term pregnancy before age of 30 years**
- **Breast feeding
(protective if total breast feeding time exceeds 1.5–2 years)**

2b B

2b B

2b B

3a B

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Parity and Breast Cancer Risk

Ma et al. Breast Cancer Research 2006, 8:R43

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Prevention by Changing Lifestyle

Factors: Body Mass Index / Diet

Oxford / AGO
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- **Maintaining normal weight**
(BMI at 18,5 – 25 kg/m²)
 - Premenopausal 3a B ++
 - Postmenopausal 2a B ++

- **Prevention/Screening and treatment of diabetes mellitus Type II**
(reduction of breast cancer incidence and mortality) 2b B ++

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Prevention by Changing Lifestyle Factors: Diet

**Oxford / AGO
LoE / GR**

Dietary patterns

- Mediterranean prudent / healthy > Western unhealthy

2b B +

Dietary components

- Fat reduced food
- Vitamins, minerals, tracer elements
- Vitamin D substitution for prevention
- Vegetables / fruits
- Phytoestrogens / Soya
- Fiber containing food

2a B +

2a B +/-

3a B +/-

2a B +/-

2a B +/-

1b A +

Prevention by Modifying Lifestyle Risk Factors: Alcohol

Oxford / AGO
LoE / GR

- **Reduction of alcohol intake reduces risk of breast cancer** **2b B**

Particularly for

- **ER+/PgR+ tumors** **2b B**
- **Invasive lobular tumors** **2b B**

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

Oxford / AGO

LoE / GR

➤ **Physical exercise**

2a⁽⁻⁾ B ++

**(Metabolic equivalents to 3–5 hrs
moderate pace walking per week)**

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women



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- **Avoiding hormonal therapy in postmenopausal women**
 - **Avoiding estrogen / progestin combinations**
 - **Avoiding estrogens only**
(no enhanced breast cancer risk with estrogen only therapy, maybe even risk reduction, but increased risk for endometrial cancer)

1b A +

1b A +/-

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Hormone (EGC) in der Post-MP

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| | N | MC-RR(95%CI) | Weitere Aussagen |
|--|--|--------------------------------|--|
| WHI WHI: JAMA 2002 | ~ 27 000 | 1.3 (1,0-1,6) | 1,3 (1,1-1,6) Koronare Events 1,4 (1,1-1,9) Schlaganfälle 2,1 (1,4-3,3) Lungenembolien 2,1 (1,5-2,9) Thrombosen |
| HERS Hulley S: JAMA 2002 | I 2763 RCT, med. 4.1 J II 2321 open-label, 2.7J | 1.2 (0.95-1.5) | Med. Alter 67 J keine sekundäre Prävention Newkg. wie WHI + Cholzystektomien↗ |
| Million Women Beral V: Lancet 2003 | 1.084 110 ~ 50% HRT 4.1 J. follow-up | 1.66 (1.6-1.8) | EPC > E Art der Anwendung egal Einnahmedauer > 5 Jahre Tibolon RR 1.45 (1.2-1.7) |
| EPIC Int J Cancer 2010 | 1.153 747 person- years o | 1.4 (1.2-1.6) 1.8 (1.4-2.2) | E-Mono EPC > E |
| Metaanalyse Nelson HD: JAMA 2002 | 16 Studien | 1.21-1.40 | Newkg. wie WHI + |

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Further
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Chlebowski SABCS 2010

Prevention by Modifying Lifestyle Risk Factors: Oral contraception (OC)

Oxford

LoE

1a

- **Overall, OC does not significantly increase risk of cancer**
- **Risk of breast cancer may be slightly increased, risk of ovarian, endometrial cancer is decreased**

1a(–)

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Cibula et al. Human Reproduction Update, Vol.16, No.6, 631–650, 2010

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Information

References

Options for Primary Prevention: Modifiable Lifestyle Factors (2/15)

Further information:

Search:

Screened data bases: Pubmed 2005 - 2013, ASCO 2005 – 2013, SABCS 2009 – 2013, Cochrane data base (2013)

Screened guidelines:

NCI (National Cancer Institute , 2013): <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2013)

<http://www.asco.org/ASCO/Quality+Care+%26+Guidelines/Practice+Guidelines/Clinical+Practice+Guidelines/Breast+Cancer>.

CMA (Canadian Medical Association , 2012): <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

NCCN (National Comprehensive Cancer Network , 2013):

http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (download 13. Jan. 2011)

References:

General understanding of biological hypothesis upon life style factors and breast cancer risk:

Tiede B, Kang Y. From milk to malignancy: the role of mammary stem cells in development, pregnancy and breast cancer. Cell Res. 2011 Feb;21(2):245-57. Epub 2011 Jan 18.

Risk Factors for Breast Cancer (3/15)

Further information:

Individual risk factors can be classified into non-modifiable, modifiable and socially defined factors. Currently, there is good evidence that changes of some modifiable risk factors could decrease breast cancer risk substantially. That means that every woman could decrease her risk of breast cancer by healthy life style.

References:

1. Modified from American Cancer Society 2011 (<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>, download 13.1.2011)
2. Ritte et al. 2013 Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer 2013 Dec 9;13:584. doi: 10.1186/1471-2407-13-584.

Risk Factors for Breast Cancer Risk (4/15)

Further information:

Nearly all possible factors of environment, nutrition, modern lifestyle and profession have been investigated regarding possible influence on breast cancer risk. Obesity and severe underweight are significant risk factors for breast cancer. However most of these studies were small cohort or case control studies with a grade IIb to V at the scale of medical evidence. Therefore the conclusions were mostly controversial or inconclusive.(1)

It is well known, how complicated it is to carry out well-designed and well-performed prospective randomized studies to investigate the effect of a single criteria (for instance fat reduced food) on breast cancer risk. Other factors, which could influence the individual risk, are genetic polymorphisms in metabolizing (e.g. alcohol, nicotin) or interactions between healthy and unhealthy effects of a single substance (e.g. phytoestrogens have different estrogenic effects and might include pesticides). Further questions of preventive intervention trails include:

- at which point in life time should intervention start or
- how long should intervention last,
- how long must the follow-up last and
- is the measured parameter (e.g. decreased vitamins level) the cause or the result of the disease.(2)

References:

1. American Cancer Society 2010 (<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>, download 13.1.2011)
2. Gerber B: Nutrition and lifestyle factors on the risk of developing breast cancer. Breast Cancer Res Treat. 2003 May;79(2):265-76.
3. Edvardsen K, Veierød MB, Brustad M, Braaten T, Engelsen O, Lund E. Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk. Int J Cancer. 2011 Mar 15;128(6):1425-33. doi: 10.1002/ijc.25463.
4. B. Hyatt, Breast Cancer Risk and the Environment (SABCS 2011)
5. MF Forman, Environment and Breast Cancer (SABCS 2011)

Food, Nutrition, Physical Activity, and the Prevention of Cancer (5/15)

No further information

No references

Prevention by Changing Pregnancy Related Factors (6/15)

Further information:

It is well known that reproductive factors are correlated with the risk of breast cancer. A meta-analysis of 47 epidemiological studies investigated breastfeeding patterns and other aspects of childbearing.(1) Women with breast cancer had, on average, fewer births (2.2 vs 2.6), ever (71% vs 79%) and shorter breastfed (9.8 vs 15.6 months) than did controls. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9-5.8; $p<0.0001$) for every 12 months of breastfeeding in addition to a decrease of 7.0% (5.0-9.0; $p<0.0001$) for each birth. It is estimated that the cumulative incidence of breast cancer in developed countries would be halved (from 6.3 to 2.7% by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently. The effect of parity on a woman's long-term risk of breast cancer is modified by age at first full-term pregnancy and by duration of breastfeeding.(2,3) An assumed risk increase in ever having breast-fed girls could not be confirmed. (4)

References:

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002;360:187-95.
2. Lord SJ: Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: a case-control study. *Cancer Epidemiol Biomarkers Prev.* 2008 Jul;17(7):1723-30.
3. Ma H: Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res.* 2006;8(4):R43.
4. Martin RM: Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. *J Natl Cancer Inst.* 2005 Oct 5;97(19):1446-57.
5. Ma H, Henderson KD, Sullivan-Halley J, Duan L, Marshall SF, Ursin G, Horn-Ross PL, Largent J, Deapen DM, Lacey JV Jr, Bernstein L. Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast

cancer among postmenopausal women in the California Teachers Study cohort. *Breast Cancer Res.* 2010;12(3):R35.

6. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res.* 2006;8(4):R43.
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8. Shinde SS, Forman MR, Kuerer HM, Yan K, Peintinger F, Hunt KK, Hortobagyi GN, Pusztai L, Symmans WF. Higher parity and shorter breastfeeding duration: association with triple-negative phenotype of breast cancer. *Cancer.* 2010 Nov 1;116(21):4933-43.
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Parity and Breast Cancer Risk (7/15)

No further information

No references

Prevention by Changing Life Style Factors: Body Mass Index / Diet (8/15)

Further information:

Overweight (BMI 25-30 kg/m²) and obesity (Grade I 30 – 35, Grade II 35 – 40 Grade III \geq 40) were found to be strong risk factor for postmenopausal breast cancer. In premenopausal pts. an inverse relationship was observed between BMI and breast cancer risk. In line with this relationship adult weight gain presented another risk factor for postmenopausal breast cancer. (1,8) In the EPIC-cohort study an a meta-analysis the relation of health (mediterranean) versus unhealthy (western) dietary patterns was examined. The breast cancer risk was significantly decreased in the highest compared to the lowest categories of mediterranean dietary patterns (OR 0.89; 95% CI: 0.82–0.99, p = 0.02), whereas there were no differences observed for western dietary patterns.(2-4) With exception of total fat intake, which might increase BMI and by that the breast cancer risk, there is no convincing data, that fruits/vegetables, micronutrition, tracer elements or vitamins intake reduced the breast cancer risk. (1,5-8) . Prevention of diabetes mellitus type II could reduce breast cancer incidence and – mortality (12).

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12. Chlebowski RT, McTiernan A, Wactawski-Wende J et al., Diabetes, metformin and breast cancer in postmenopausal women, JCO 2012 Aug 10; 30 (23):2844-52

Prevention by Changing Life Style Factors: Diet (9/15)

No further information

No references

Prevention by Modifying Life Style Risk Factors: Alcohol (10/15)

Further information:

Ethanol itself is not a carcinogen, but it is metabolized to potential carcinogenic compounds, for example, acetaldehyde. Alcohol induces oxidative stress in the liver so that other carcinogenic substances can be synthesized through enzyme induction, but cannot be metabolized. Alcohol increases the permeability of cell membranes thus facilitating the traffic of carcinogens into the cells. It also induces the proliferation of mammary epithelia in animal models and is resulting in higher serum concentrations of estradiol in premenopausal women. An established link to breast cancer would be of great interest since this noxious agent could be avoided easily.(1) A meta-analysis including 58,515 women with invasive breast cancer and 95,067 controls from 53 studies estimated the relative risks of breast cancer after stratifying by study, age, parity and, where appropriate, women's age when their first child was born and consumption of alcohol and tobacco. Compared with women who reported drinking no alcohol, the relative risk of breast cancer was 1.32 (1.19-1.45, $P<0.00001$) for an intake of 35-44 g per day alcohol, and 1.46 (1.33-1.61, $P<0.00001$) for ≥ 45 g per day alcohol. The relative risk of breast cancer increased by 7.1% (95% CI 5.5-8.7%; $P<0.00001$) for each additional 10 g per day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis.(5) A further meta-analysis of 98 unique studies involving 75,728 and 60,653 cases in drinker versus non-drinker and dose-response analyses revealed an association with alcohol drinking by 22% (95% CI: 9-37%); each additional 10 g ethanol/day was associated with risk higher by 10% (95% CI: 5-15%). (4) Alcohol use may be more strongly associated with risk of hormone-sensitive breast cancers than hormone-insensitive subtypes, suggesting distinct etiologic pathways for these two breast cancer subtypes.(2,3) Alcohol consumption is consistently associated with increased breast density, which is associated with increased breast cancer risk. (6). Especially alcohol consumption before first pregnancy seems to be associated with increased risks of proliferative BBD and breast cancer. (6)

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Prevention by Modifying Life Style Risk Factors: Physical Activity (11/15)

Further information:

The preventive effect of physical exercise is explained by nonspecific immune stimulation and decreased estrogen levels during recovery and reduction of BMI.(1) Most studies found that exercise, weight reduction, low-fat diet, and reduced alcohol intake were associated with a decreased risk of breast cancer.(2) A review of 34 case-control and 28 cohort studies examined the different parameters of physical activity regarding the risk of breast cancer. Effect modification of this association by menopausal status, body mass index (BMI), racial group, family history of breast cancer, hormone receptor status, energy intake and parity were also considered.

Evidence for a risk reduction associated with increased physical activity was found in 47 (76%) of 62 studies with an average risk decrease of 25-30%. A dose-response effect existed in 28 of 33 studies. Stronger decreases in risk were observed for recreational activity, lifetime or later life activity, vigorous activity, among postmenopausal women, women with normal BMI, non-white racial groups, those with hormone receptor negative tumours, women without a family history of breast cancer and parous women.(2,3)

The *metabolic equivalent of task (MET)*, or simply *metabolic equivalent*, is a physiological concept expressing the energy cost of physical activities as multiples of resting metabolic rate (RMR) and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference rate of metabolic rate at rest, set by convention to 3.5 ml O₂·kg⁻¹·min⁻¹ or equivalently 1 kcal·kg⁻¹·h⁻¹ or 4.184 kJ·kg⁻¹·h⁻¹. By convention 1 MET is considered as the resting metabolic rate obtained during quiet sitting. MET values of physical activities range from 0.9 (sleeping) to 18 (running at 17.5 km/h or a 5:31 mile pace). (<http://en.wikipedia.org>)

A meta-analysis of prospective studies regarding the association between physical activity and breast cancer risk confirmed the assumption, that physical activity could significantly reduce the risk of breast cancer. Overall, the combined relative risk (RR) with 95 % CI of breast cancer was 0.88 (0.85-0.91) in 31 studies with 63,786 cases. In subgroup analysis by activity type, data from 27 studies including 37,568 cases for non-occupational activity (including recreational activity and household activity) and seven studies including 28,268 cases for occupational activity were used, and the RR (95 % CI) of breast cancer was 0.87 (0.83-0.91) and 0.90 (0.83-0.97), respectively. The inverse association was consistent among all subgroups analyses. Stronger association was found for subjects with BMI <25 kg/m² [0.72 (0.65-0.81)], premenopausal women [0.77 (0.72-0.84)], and estrogen and progesterone receptor-negative breast cancer [0.80 (0.73-

0.87)]. Dose-response analysis suggested that the risk of breast cancer decreased by 2 % ($P < 0.00$) for every 25 metabolic equivalent (MET)-h/week increment in non-occupational physical activity, 3 % ($P < 0.00$) for every 10 MET-h/week (roughly equivalent to 4 h/week of walking in 2 miles/h or 1 h/week of running in 6 miles/h) increment in recreational activity, and 5 % ($P < 0.00$) for every 2 h/week increment in moderate plus vigorous recreational activity, respectively. (4)

References:

1. Gerber B: Nutrition and lifestyle factors on the risk of developing breast cancer. *Breast Cancer Res Treat.* 2003 May;79(2):265-76
2. Cummings SR: Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst.* 2009 Mar 18;101(6):384-98.
3. Friedenreich CM: Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. *Br J Sports Med* 2008 42: 636-647
4. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat.* 2013 Feb;137(3):869-82. doi: 10.1007/s10549-012-2396-7. Epub 2012 Dec 30.

Prevention by Modifying Life Style Risk Factors: Hormone Therapy in Postmenopausal Women (12/15)

Further information:

The use of (HRT) has been shown to be associated with increased risk of BC. For HRT, evidence from randomized controlled trials and observational studies has shown that women using post-menopausal hormone replacement therapy (HRT) are at an increased risk of BC (1,2,3) Moreover, the risk of BC associated with HRT is larger for users of combined HRT than for users of estrogen-only therapy, who may not be at increased risk at all. (1,4,5) In the Women's Health Initiative randomized, placebo-controlled trial, estrogen plus progestin was associated with greater breast cancer incidence, and the cancers were more commonly node-positive. Breast cancer mortality also appeared to be increased with combined use of estrogen plus progestin (1,4). In a Norwegian study current users had a risk twice as high as never-users. The use of combination therapy for more than five years tripled risk. Estradiol only use did not cause a statistically significant increase in risk (5).

According to a cohort study and metaanalysis the relative risks of invasive breast cancer in current users compared with never users of hormone therapy varied significantly according to tumour histology overall, the effects of hormone therapy on invasive ductal, lobular, and tubular cancer were generally greater for oestrogen-progestagen therapy than for oestrogen-only therapy, and were attenuated with increasing body-mass index (BMI) (3).

Studies from several countries show that the decline in the use of hormone therapy, following the publication of the WHI results, is followed by a decline in breast cancer incidence (5,6).

According to the results of the WHI randomized trials use of conjugated equine estrogens (CEE) alone (given only to women without uterus), younger women (aged 50-59 years) had more favorable results for all-cause mortality, myocardial infarction, and the global index. Absolute risks of adverse events (measured by the global index) per 10,000 women annually taking CEE plus MPA ranged from 12 excess cases for ages of 50-59 years to 38 for ages of 70-79 years; for women taking CEE alone, from 19 fewer cases for ages of 50-59 years to 51 excess cases for ages of 70-79 years. Quality-of-life outcomes had mixed results in both trials. Findings from the intervention and extended postintervention follow-up of the 2 WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women (7).

References:

1. Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, et al. (2010) Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 304: 1684–1692
2. Beral V, Reeves G, Bull D, Green J; for the Million Women Study Collaborators. Breast Cancer Risk in Relation to the Interval Between Menopause and Starting Hormone Therapy. J Natl Cancer Inst. 2011 Jan 28.
3. Reeves GK, Beral V, Green J, Gathani T, Bull D (2006) Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol 7: 910–918.
4. Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, Manson JE, Stefanick ML, Ockene J, Sarto GE, Johnson KC, Wactawski-Wende J, Ravdin PM, Schenken R, Hendrix SL, Rajkovic A, Rohan TE, Yasmeeen S, Prentice RL; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010 Oct 20;304(15):1684-92.
5. Saether S, Bakken K, Lund E (2012) The risk of breast cancer linked to menopausal hormone therapy. Tidsskr Nor Laegeforen 132: 1330–1334
6. De P, Neutel CI, Olivotto I et al. Breast cancer incidence and hormone replacement therapy in Canada. J Natl Cancer Inst 2010; 102: 1489 – 95
7. Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68. doi: 10.1001/jama.2013.278040.

Menopausal Hormone Therapy Influence on Incidence and Related Mortality of Selected Cancer (Chlebowski et al SABCS 2010, abstr. S6-1)

| | E Alone | E+P |
|---------------|------------------|-------------------|
| | HR (95% CI) | HR (95% CI) |
| Breast Cancer | | |
| Incidence | 0.80 (0.62-1.04) | 1.24 (1.01, 1.54) |

| | | |
|-------------------|-------------------|-------------------|
| Death from | Not reported | 1.96 (1.00, 4.06) |
| Colorectal Cancer | | |
| Incidence | 1.12 (0.77, 1.63) | 0.56 (0.38, 0.81) |
| Death after | 0.99 (0.50, 1.96) | 1.54 (0.82, 2.87) |
| NSCLC | | |
| Incidence | 1.10 (0.74, 1.64) | 1.23 (0.92, 1.63) |
| Death from | 0.89 (0.52, 1.52) | 1.87 (1.22, 2.88) |

Chlebowski JAMA 2003;289:3243, Chlebowski NEJM 2004;350:991, Stefanick JAMA 2006;242:1048, Ritenbaugh Cancer Epi Bio Prev 2008;17:2609, Prentice Cancer Epi Bio Prev 2009;18:1531, Chlebowski NEJM 2009;360:573, Chlebowski Gynecologic Oncology 2010;117:394; abst, Chlebowski Proc ASCO 2010;abst 1705

Prevention - Hormone (EGC) in der Post-MP (13/15)

No further information

No references

Prevention by Modifying Life Style Risk Factors: Oral contraception (14/15)

Further information and references:

For the risk of use of oral contraceptives currently best comprehensive analysis can be obtained from:

D. Cibula, A. Gompel, A.O. Mueck, C. La Vecchia, P.C. Hannaford, S.O. Skouby, M. Zikan, and L. Dusek. Hormonal contraception and risk of cancer. Human Reproduction Update, Vol.16, No.6 pp. 631–650, 2010

Thus, we are citing the Conclusions of this paper:

“In a majority of studies there is no increase in the risk of breast cancer reported in OC users. When the RR was shown to be increased, this effect disappeared progressively after stopping OC use. Long duration of OC use at a young age before the FFTP seems to be the most important risk factor, as hormones act on a less differentiated tissue. The number of events attributable to OC use remains below 1% of the total breast cancers and 7% for premenopausal breast cancer if the RR of the Oxford meta-analysis is applied to calculate the attributable fraction of breast cancer in France (CGHFBC, 1996). The level of the increase in the RR is so low that it is not fully convincing and may have concerned the first generation of OC formulations. Although the modest and inconsistent associations may be attributable to variation in study design, it is also possible that they result from disease heterogeneity. Furthermore, significant involvement of screening or recall bias cannot be excluded (Marchbanks *et al.*, 2002; Rosenberg *et al.*, 2009; Shapiro, 2009). None of these studies has shown a role for the composition of OC on breast cancer risk. The possible, whereas currently unconfirmed, small increase in the risk of breast cancer in OC users with BRCA1/2 mutations is strongly counterbalanced by the benefits in terms of ovarian cancer protection.”

A recent systematic review concluded, that breast cancer incidence was slightly but significantly increased in OC users (OR, 1.08; CI, 1.00-1.17); results show a higher risk associated with more recent use of oral contraceptives. Risk of cervical cancer was increased with duration of oral contraceptive use in women with human papillomavirus infection. Colorectal cancer (OR, 0.86; CI, 0.79-0.95) and endometrial cancer incidences (OR, 0.57; CI, 0.43-0.77) were significantly reduced by oral contraceptive use. Compared with never use, ever use of oral contraceptives is significantly associated with decreases in colorectal and endometrial cancers and small increases in breast cancers (1).

A systematic review and meta-analysis on the association of oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women (BRCA mutation carriers) suggest that associations between ever use of OCs and ovarian and breast cancer among women who are BRCA1 or BRCA2 mutation carriers are similar to those reported for the general population (2).

1. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, Dinan M, McBroom AJ, Hasselblad V, Sanders GD, Myers ER. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev.* 2013 Nov;22(11):1931-43. doi: 10.1158/1055-9965.EPI-13-0298. Epub 2013 Sep 6.
2. Moorman PG, Havrilesky LJ, Gierisch JM. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *J Clin Oncol.* 2013 Nov 20;31(33):4188-98. doi: 10.1200/JCO.2013.48.9021. Epub 2013 Oct 21.

OC and Breast Cancer Risk (15/15)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Risk and Prevention

Breast Cancer Risk and Prevention

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- **Versions 2003–2013:**
**Schmutzler with Albert / Blohmer / Fehm /
Kiechle / Maass / Mundhenke / Thomssen**
- **Version 2014:**
Schmutzler / Rody

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Principles in Prevention

- Women at increased risk for breast cancer are not considered *patients* but *healthy women* or *counselees*
- A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures
- Highest priority: „First, do no harm!“
(*Primum nil nocere*)

Who Should be Tested for BRCA1/2 Mutations?

Oxford LoE: 2b GR: B AGO: ++

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Families with

**at least three women with breast cancer independent of age or
at least two women with breast cancer, one < 51 yrs. or
at least one woman affected by breast and one by ovarian cancer or
at least one woman affected by breast and ovarian cancer or
at least two women affected by ovarian cancer or
at least one woman affected by bilateral breast cancer, first < 51 yrs. or
at least one woman affected by breast cancer < 36 yrs. or
at least one man affected by breast cancer and one additional relative
affected by breast or ovarian cancer* #**

*** in one side of the family**

Further
Information

References

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate $\geq 10\%$ in ~17.000 families tested by 2013

Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013

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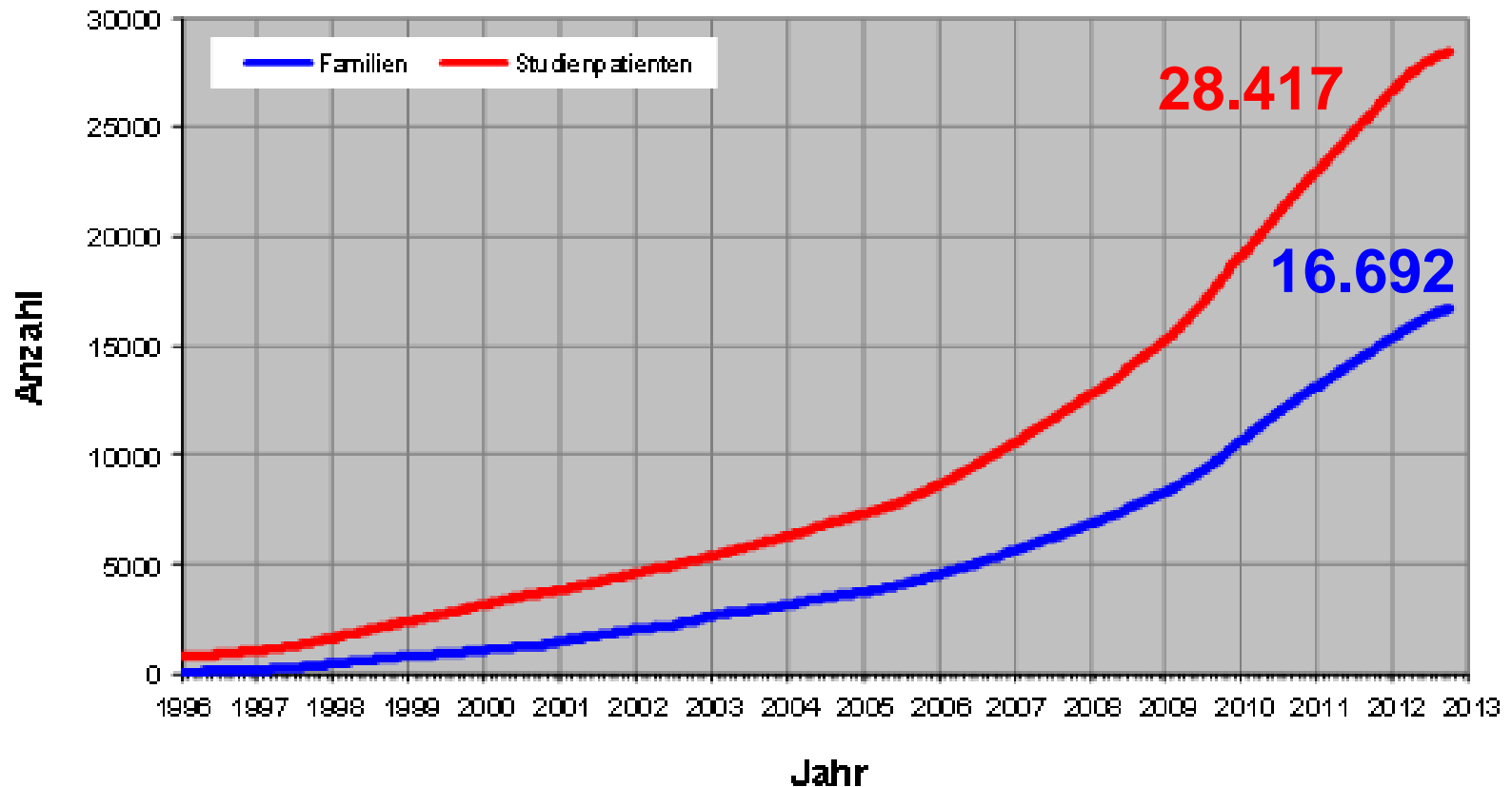
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Suggested Use of a Screening Checklist *

Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs

Name der Patientin:

Geburtsdatum:

A. Patientin und deren Geschwister / Kinder

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei der Patientin <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei der Patientin <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei der Patientin, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin <u>nach</u> dem 50. LJ | | 1 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin | | 2 | |
| eines Mamma-Karzinoms bei Schwestern/Töchtern <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei Schwestern/Töchtern, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei Schwestern/Töchtern <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei Brüdern/Söhnen | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei Schwestern/Töchtern | | 2 | |
| Summe Patientin / Geschwister / Kinder | | A | |

B. Mütterliche Linie

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei einem angehörigen Mann | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen | | 2 | |
| Summe mütterliche Linie | | B | |

C. Väterliche Linie

| Auftreten | Anzahl | Gewichtung | Ergebnis |
|---|--------|------------|----------|
| eines Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 36. LJ | | 3 | |
| eines unilateralen Mamma-Karzinoms bei einer Angehörigen <u>vor</u> dem 51. LJ | | 2 | |
| eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste <u>vor</u> dem 51. LJ | | 3 | |
| eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen <u>nach</u> dem 50. LJ | | 1 | |
| eines Mamma-Karzinoms bei einem angehörigen Mann | | 2 | |
| eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen | | 2 | |
| Summe väterliche Linie | | C | |

D. Der höhere Wert aus B und C

D

E. Summe aus A und D = Risiko-Score

A+D

Ausfüllhinweis

Zunächst wird die Anzahl bekannter Erkrankungsfälle bei den Geschwistern und Kindern, einschließlich der aktuellen Erkrankung der Patientin sowie in der mütterlichen und väterlichen Linie erfragt.

Diese Zahlen werden mit den jeweiligen Gewichtungen multipliziert. Dann wird die Summe aus diesen Ergebnissen errechnet und in die Felder A und B und C eingetragen.

Der höhere der beiden Werte aus den Feldern B und C wird in Feld D eingetragen.

Der Gesamtscore errechnet sich dann aus der Summe der Felder A und D.

Eine Risikoberatung in den ausgewiesenen Zentren ist bei Scores ≥ 3 Punkten zu empfehlen.

Version: 03. Dezember 2012 (C) Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs

*online tool provided by the Ärztekammer Westfalen-Lippe based on the inclusion criteria of the GC-HBOC
www.aekwl.de/brustzentren-download

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Variants of Unknown Significance (VUS): 5-30% of all BRCA1/2 Mutations Detected

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Proposed Classification System for Sequence Variants Identified
by Genetic Testing

| Class | Description | Probability of being pathogenic |
|-------|--|---------------------------------|
| 5 | Definitely pathogenic | > 0.99 |
| 4 | Likely pathogenic | 0.95–0.99 |
| 3 | Uncertain | 0.05–0.949 |
| 2 | Likely not pathogenic or of little clinical significance | 0.001–0.049 |
| 1 | Not pathogenic or of no clinical significance | < 0.001 |

Testing Recommendations Associated With Each Class of Variant

| Class | Clinical testing | Surveillance recommendations if at-risk relative is positive | Research testing of family members |
|-------|---|--|--|
| 5 | Test at-risk relatives for variant | Full high-risk surveillance guidelines | Not indicated |
| 4 | Test at-risk relatives for variant ^a | Full high-risk surveillance guidelines | May be helpful to further classify variant |
| 3 | Do not use for predictive testing in at-risk relatives ^a | Based on family history (and other risk factors) | May be helpful to further classify variant |
| 2 | Do not use for predictive testing in at-risk relatives ^a | Treat as “no mutation detected” for this disorder | May be helpful to further classify variant |
| 1 | Do not use for predictive testing in at-risk relatives ^a | Treat as “no mutation detected” for this disorder | Not indicated |

^aRecommend continuing to test proband for any additional testing modalities available for the disorder in question; e.g., rearrangement testing.

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(Plon et al., Human Mutation, 2008)

VUS: Problems and Questions

- Most VUS are private (>60%) or extremely rare (≤ 3 , >80%)
- Additional analyses required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurrence analysis, large case / control studies
- *in silico* prediction tools (PolyPhen2, SIFT) are not adequate for clinical decision making
- VUS classification and clinical decision making are not standardized

State of the Art

Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

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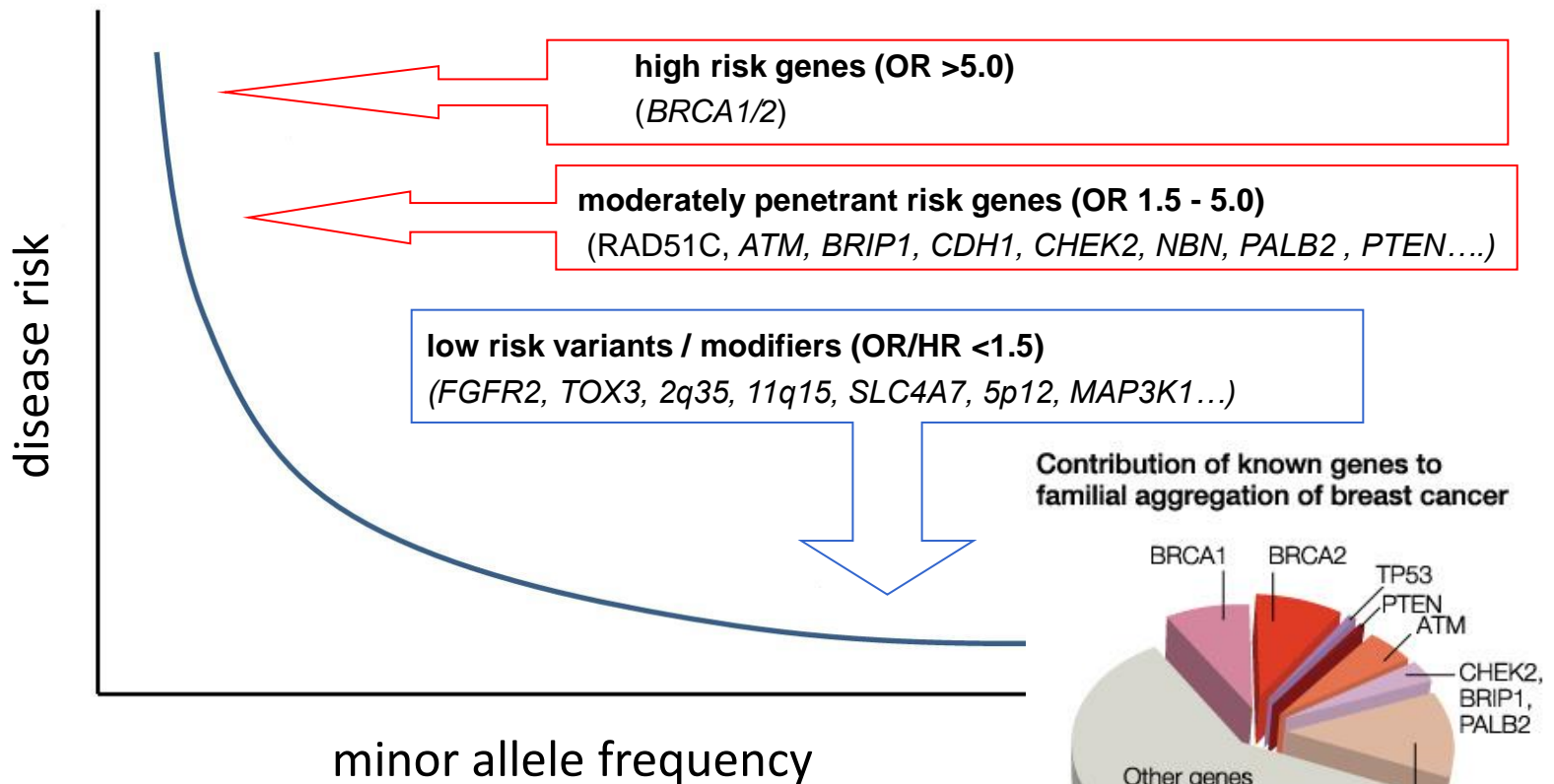
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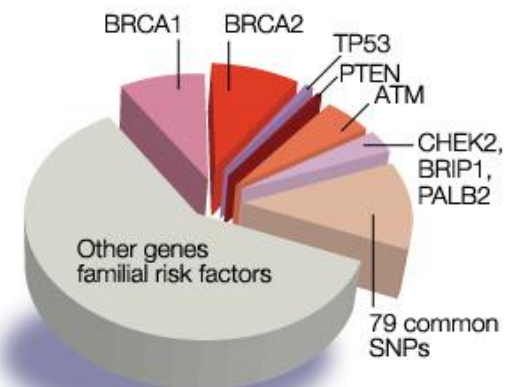
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Contribution of known genes to
familial aggregation of breast cancer



Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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| Syndrome | Gene alteration | Lifetime Risk BC |
|--|--|---|
| Li Fraumeni | p53 | ~ 50 % ¹ |
| Cowden | PTEN | ~ 25 % ² |
| Hereditary diffuse gastric cancer syndrome | CDH1 | ~40-50 % (lobular) ³ |
| Peutz-Jeghers Syndrome | STK11/ LKB1 | ~45-50 % ⁴ Ovary: ~20 % Cervix: ~10 % Uterus: ~10 % |
| Lynch | mismatch repair MLH1, MSH2, MSH6, PMS2 | up to twofold increased risk compared to general population ⁵ Endometrial: ~ 25-60 % Ovary: up to 25 % |

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References

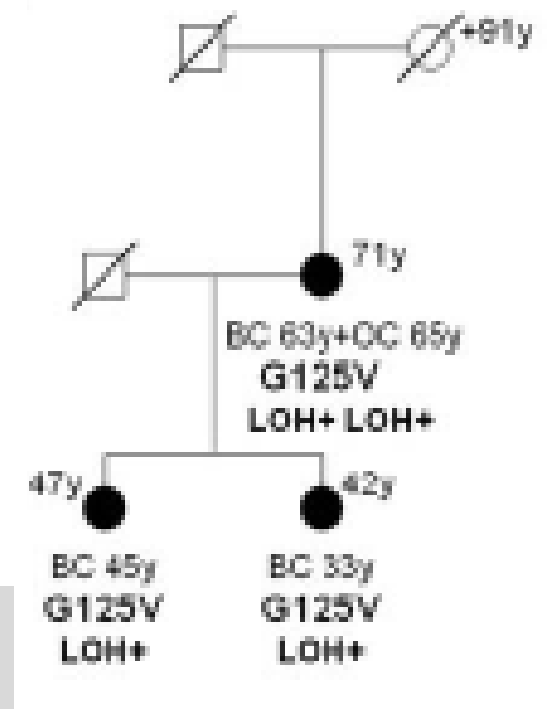
Recommendation: genetic counselling: GCP

Third Moderate to High Risk Gene Identified within the GC-HBOC

Germ-line mutations in breast and ovarian cancer pedigrees establish *RAD51C* as a human cancer susceptibility gene

Nature Genetics April 18, 2010

Alfons Meindl¹, Heide Hellebrand^{1*}, Constanze Wiek^{2*}, Verena Erven², Barbara Wappenschmidt³, Dieter Niederacher⁴, Marcel Freund², Peter Lichtner⁵, Linda Hartmann⁶, Heiner Schaal⁶, Juliane Ramser¹, Ellen Honisch⁴, Christian Kubisch⁷, Hans E. Wichmann⁸, Karin Kast⁹, Helmut Deißler¹⁰, Christoph Engel¹¹, Bertram Müller-Myhsok¹², Kornelia Neveling¹³, Marion Kiechle¹, Christopher G. Mathew¹⁴, Detlev Schindler¹³, Rita K. Schmutzler³⁺, Helmut Hanenberg^{2,15+}



- 1.100 BRCA1/2 negative risk families:
670 breast only, 430 breast and ovarian cancer
- 6 deleterious mutations in BC/OC families only (**1.5%**)

Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

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BROCA 40 gene panel (cross-cancer, <http://web.labmed.washington.edu/tests/genetics/BROCA>)

APC
ATM
ATR
BAP1
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK1
CHEK2
EPCAM
FAM175A
GALNT12
GEN1
GREM1
HOXB13
MLH1
MRE11A
MSH2
MSH6
MUTYH
NBN
PALB2
PMS2
PRSS1
PTEN
RAD50
RAD51
RAD51C
RAD51D
RET
SMAD4
STK11
TP53
TP53BP1
VHL
XRCC2

AMBRY Genetics BreastNext (16 genes) <http://www.ambrygen.com/tests/breastnext>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
MRE11A
MUTYH
NBN
PALB2
PTEN
RAD50
RAD51C
STK11
TP53

CEGAT CAN02: Brust- und Ovarialkarzom (30 genes) http://www.cegat.de/Tumorerkrankungen_171.html

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
EPCAM
FANCA
FANCC
FANCD2
FANCE
FANCF
FANGC
MEN1
MLH1
MRE11A
MSH2
MSH3
MSH6
NBN
PALB2
PMS1
PMS2
PTCH1
PTEN
RAD50
RAD51C
STK11
TP53

TruSight™ Cancer (Illumina) http://res.illumina.com/documents/products/5Cdatasheets/5Cdatasheet_trusight_cancer.pdf

AIP
ALK
APC
ATM
BAP1
BLM
BMPR1A
BRCA1
BRCA2
BRIP1
BUB1B
CDC73
CDH1
CDK4
CDKN1C
CDKN2A
CEBPA
CEP57
CHEK2
CYLD
DDB2
DICER1
DIS3L2
EGFR
EPCAM
ERCC2
ERCC3
ERCC4
ERCC5
EXT1
EXT2
EZH2
FANCA
FANCB
FANCC
FANCD2
FANCE
FANCF
FANGC
FANCI
FANCL
FANCM
FH
FLCN
GATA2
GPC3
HNF1A

HRAS
KIT
MAX
MEN1
MET
MLH1
MSH2
MSH6
MUTYH
NBN
NF1
NF2
NSD1
PALB2
PHOX2B
PMS1
PMS2
PRF1
PRKAR1A
PTCH1
PTEN
RAD51C
RAD51D
RB1
RECQL4
RET
RHBDF2
RUNX1
SBDS
SDHAF2
SDHB
SDHC
SDHD
SLX4
SMAD4
SMARCB1
STK11
SUFU
TMEM127
TP53
TSC1
TSC2
VHL
WRN
WT1
XPA
XPC

CENTOGENE BC/OC panel (16 genes) <https://www.centogene.com/centogene>

ATM
BARD1
BRCA1
BRCA2
BRIP1
CDH1
CHEK2
MRE11A
MSH6
NBN
PALB2
PTEN
RAD51
RAD51C
STK11
TP53

MYRIAD myRISK Panel (25 genes)

APC
ATM
BARD1
BMPR1A
BRCA1
BRCA2
BRIP1
CDH1
CDK4
CDKN2A
CHEK2
EPCAM
MLH1
MSH2
MSH6
MUTYH
NBN
PALB2
PMS2
PTEN
RAD51C
RAD51D
SMAD4
STK11
TP53

Low risk Variants from Genome Wide Association Studies (GWAS)

| Locus | SNP | Häufigkeit | TOTAL BCAC | | FRR (%) |
|--------------|------------------|------------|-------------|---------------------------|-------------|
| | | | Odds Ratio | P-trend | |
| FGFR2 | rs2981582 | 38% | 1.24 | 5x10⁻⁸⁷ | 1.6% |
| TOX3 | rs3803662 | 25% | 1.21 | 8x10⁻⁵² | 1.1% |
| 2q35 | rs13387042 | 51% | 1.12 | 3x10 ⁻³⁴ | 0.5% |
| 11q15 | rs614367 | 15% | 1.20 | 5x10 ⁻¹⁶ | 0.5% |
| SLC4A7 | rs4973768 | 46% | 1.11 | 4x10 ⁻²³ | 0.4% |
| 5p12 | rs10941679 | 26% | 1.12 | 4x10 ⁻²³ | 0.4% |
| MAP3K1 | rs889312 | 28% | 1.11 | 3x10 ⁻²⁰ | 0.3% |
| 8q24 | rs13281615 | 40% | 1.10 | 8x10 ⁻¹⁵ | 0.3% |
| CASP8 | rs1045485 | 13% | 0.9 | 2x10 ⁻⁸ | 0.2% |
| ESR1 | rs2046210 | 33% | 1.09 | 2x10 ⁻¹⁵ | 0.2% |
| LSP1 | rs3817198 | 30% | 1.08 | 5x10 ⁻¹¹ | 0.2% |
| 1p11.2 | rs11249433 | 39% | 1.10 | 7x10 ⁻¹⁰ | 0.2% |
| ZNF365 | rs10995190 | 15% | 0.88 | 4x10 ⁻¹⁵ | 0.2% |
| ZMIZ1 | rs704010 | 39% | 0.92 | 3x10 ⁻⁸ | 0.1% |
| CDKN2A/B | rs1011970 | 17% | 1.08 | 7x10 ⁻⁸ | 0.09% |
| COX11 | rs6504950 | 27% | 0.95 | 10 ⁻⁸ | 0.07% |
| ANKRD16 | rs2380205 | 43% | 0.98 | 4x10 ⁻⁷ | 0.01% |
| RAD51L1 | rs999737 | 24% | 0.94 | 2x10 ⁻⁷ | 0.01% |

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Low Risk Variants as Modifiers

Retrospective

Gaudet et al., in coop with GC-HBOC 2013: Combined genotype distribution of **14 variants** in 8,221 **BRCA2** mutation carriers (FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13)

- **Couch et al. in coop with the GC-HBOC 2013:** Combined genotype distribution of **10 variants** in 11,705 **BRCA1** mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1, TERT)
- 5% of BRCA1 carriers at lowest risk (28–50%) compared to the 5% at highest risk (81–100%)

Prospective

Mavaddat et al., 2013: combined genotype distribution of 7 low-risk SNP in **909 BRCA2 carriers**

BRCA2 carriers at the highest tertile of the score distribution were at significantly higher risk than women at the lowest tertile (HR = 4.1, 95%; CI = 1.2 to 14.5; P = .02)

first ‘proof of principle’

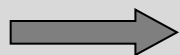
Associations are breast cancer subtype specific

Garcia-Closas et al., Clin Cancer Res, 2008

Genetically Defined Subtypes are Distinct Tumor Entities

Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:

- Typical histopathological features?
- Sensitivity to current screening modalities?
- Better survival of early detected tumors?
- Natural disease course?
- Response to anti-tumor therapy?



Genotype-phenotype-correlations must be employed

Current Clinical Impact of Other Risk Genes

The remaining cancer susceptibility is most likely be transmitted by an oligo- or polygenic trait of moderate and low risk genes and alleles.

Moderate risk genes such as *RAD51C* exhibit very low mutation detection rates and may be associated with specific tumor subtypes.

Low risk variants confer only small risk elevations and also seem to be associated with specific tumor subtypes. Potential multiplicative effects that may be relevant for risk stratification and the provision of clinical prevention strategies remain to be elucidated.

Therefore genetic testing of moderate and low risk genes and variants should only be performed within large prospective cohort studies like the German Consortium for Hereditary Breast and Ovarian Cancer GC-HBOC.

Oxford / AGO LoE / GR

Clinical genetic testing for *RAD51C*; *CHEK2*

and/or other moderate risk genes, e.g. gene panels

2b **B** -

Clinical genetic testing for low risk variants

3b **D** --

Referral to centres of the GC-HBOC

5 **D** ++

or cooperating centres

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing

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- The risk collective is clearly defined by risk criteria
- The positive predictive value of risk criteria with respect to the identification of the genetic risk factor is known
- The cut-off values for genetic testing evolved through a transparent consensus process
- The genetic test is valid and reliable
- A spectrum bias is excluded or defined
- A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease

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Non Directive Counseling for the Uptake of Preventive Measures

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- According to the Genetic Diagnostic Law
- According to the Medical Devices Act, e.g. risk assessment requires professional training and expertise
- Communicate absolute risks within a manageable timeframe
- Communicate competing risks, e.g. risk of progressive disease in relation to the risk of a secondary primary in case women have already been affected by primary breast cancer
- Allow for appropriate time for consideration

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Definition of Women at Moderate to High Risk

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- **Deleterious mutation in the BRCA1, BRCA2**
- **Heterozygous risk of $\geq 20\%$ or remaining life time risk of $\geq 30\%$ acc. to a validated standard risk prediction model**
- **Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)**

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1a A ++

2b B +

2a B ++

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Surveillance Program for Women with Deleterious BRCA-mutations*

**Oxford / AGO
LoE / GR**

Multimodal intensive surveillance program

For the detection of early stage breast cancers

2a B ++

- | | | |
|-------------------------------|----------------------|----------------------|
| ➤ Clinical breast exam | >=25 years | semi-annually |
| ➤ Sonography | >=25 years | semi-annually |
| ➤ Mammography | >=40 years | biannual |
| ➤ Breast MRI | >=25 years | annual |

➤ **For mortality reduction**

5 D +

***Referral to centres of the GC-HBOC or cooperating centres is recommended**

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Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

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Rationale:

- Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (8-18 years)
- Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families
- Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up

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References

Surgical Prevention for Healthy BRCA1/2 Mutation Carriers

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- **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO, PBSO) around 40 years of age**
reduces OvCa incidence and mortality
reduces BrCa incidence and mortality
reduces overall mortality
- **Risk-reducing bilateral mastectomy (RR-BM, PBM) reduces BrCa incidence and mortality**

2a B ++*

2a B +*

RR-BSO is performed after completion of family planning
RR-BM revealed a high incidence of premalignant lesions

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***Study participation recommended**

Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer

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- | | |
|--|--------------------------------|
| <ul style="list-style-type: none"> • Bilateral salpingo-oophorectomy (RR-BSO) reduces OvCa incidence and mortality reduces BrCa mortality reduces overall mortality (contradictory results for reduction of cl BrCa incidence) | 2b B ++* |
| <ul style="list-style-type: none"> • Bilateral mastectomy+ (RR-BM) reduces cl BrCa incidence | 2b B +/-* |
| <ul style="list-style-type: none"> • Tamoxifen (reduces cl BrCa incidence) | 2b B +/-* |
| <ul style="list-style-type: none"> • Indication for PBM should consider age at onset of first breast cancer and the affected gene | 2a B +++* |

+ Overall prognosis has to be considered

***Study participation recommended**

Risk-reducing Salpingo-oophorectomy and All-cause Mortality

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Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality^a

| | All Eligible Women | | | No Prior Breast Cancer ^b | | | Prior Breast Cancer ^c | | |
|---|---------------------|---------------------|---------------------|-------------------------------------|---------------------|---------------------|----------------------------------|---------------------|---------------------|
| | Total (n = 2482) | BRCA1 (n = 1587) | BRCA2 (n = 895) | Total (n = 1458) | BRCA1 (n = 935) | BRCA2 (n = 523) | Total (n = 1027) | BRCA1 (n = 654) | BRCA2 (n = 373) |
| Risk-reducing salpingo-oophorectomy | | | | | | | | | |
| Yes | 993 (40.0) | 706 (44.5) | 287 (32.1) | 447 (30.7) | 327 (35.0) | 120 (22.9) | 451 (43.9) | 317 (48.5) | 134 (35.9) |
| Deaths | 31 (3.1) | 25 (3.5) | 6 (2.1) | 8 (1.8) | 8 (2.4) | 0 | 19 (4.2) | 14 (4.4) | 5 (3.7) |
| No | 1489 (60.0) | 881 (55.5) | 608 (67.9) | 1011 (69.3) | 608 (65.0) | 403 (77.1) | 576 (56.1) | 337 (51.5) | 239 (64.1) |
| Deaths | 146 (9.8) | 93 (10.6) | 53 (8.7) | 60 (5.9) | 43 (7.1) | 17 (4.2) | 92 (16.0) | 54 (16.0) | 38 (15.9) |
| Age, mean (range), y | | | | | | | | | |
| At time of risk-reducing oophorectomy | 45.4 (20.5-79.0) | 44.5 (20.5-79.0) | 47.6 (30.4-72.9) | 43.2 (20.5-79.0) | 42.1 (20.5-79.0) | 46.4 (33.0-68.5) | 47.6 (29.7-75.2) | 47.0 (29.7-75.2) | 49.1 (30.4-72.9) |
| At start of follow-up for those without oophorectomy | 39.8 (18.1-90.4) | 38.5 (18.2-90.4) | 41.6 (18.1-82.7) | 36.3 (18.1-90.4) | 35.1 (18.2-90.4) | 38.2 (18.1-82.7) | 45.3 (21.9-86.2) | 44.2 (21.9-86.2) | 46.9 (26.1-77.7) |
| Follow-up, mean (range), y | | | | | | | | | |
| To death | 6.0 (0.5-23.5) | 5.9 (0.6-22.3) | 6.2 (0.5-23.5) | 9.0 (0.96-23.5) | 8.5 (1.0-22.3) | 10.3 (2.8-23.5) | 4.6 (0.5-20.3) | 4.3 (0.6-20.3) | 5.1 (0.5-13.3) |
| To censoring | 5.0 (0.5-27.9) | 5.0 (0.5-27.7) | 4.9 (0.5-27.9) | 5.8 (0.5-27.9) | 5.7 (0.5-27.7) | 5.9 (0.5-27.9) | 4.5 (0.5-24.6) | 4.8 (0.5-24.6) | 4.1 (0.5-15.4) |
| All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI) ^d | 0.40 (0.26-0.61) | 0.38 (0.24-0.62) | 0.52 (0.22-1.23) | 0.45 (0.21-0.95) | 0.52 (0.24-1.14) | No deaths | 0.30 (0.17-0.52) | 0.26 (0.13-0.52) | 0.45 (0.17-1.16) |
| Age <50 y | 0.41 (0.25-0.67) | 0.40 (0.24-0.68) | 0.16 (0.02-1.30) | 0.70 (0.31-1.57) | 0.50 (0.21-1.20) | No deaths | 0.28 (0.14-0.55) | 0.30 (0.14-0.64) | 0.19 (0.02-1.59) |
| Age ≥50 y | 0.37 (0.15-0.94) | 0.22 (0.06-0.85) | 0.47 (0.12-1.80) | 0.28 (0.03-2.42) | 0.93 (0.11-8.12) | No deaths | 0.37 (0.13-1.03) | 0.12 (0.02-0.73) | 0.46 (0.10-2.13) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aValues are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

^bThere were no breast cancer cases prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.

^cBreast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

^dAdjusted for year of birth and stratified by center.

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Further
Information

References

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Domchek et al. JAMA 2010; Table 4.

Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive)

Rhiem *et al. Breast Cancer Research* 2012, **14**:R156
<http://breast-cancer-research.com/content/14/6/R156>

Page 6 of 8

Table 2 Cumulative risks (in %) and 95% confidence intervals (in parentheses) for contralateral breast cancer depending on age at first breast cancer observed in relatives of index patients.

| | BRCA1 | BRCA2 | BRCA negative |
|--|------------------|------------------|------------------|
| Age at first breast cancer < 40 years | | | |
| 5 years after first breast cancer | 14.1 (10.1-18.0) | 2.9 (0.0-6.3) | 4.8 (2.6-6.9) |
| 10 years after first breast cancer | 30.1 (24.0-36.2) | 18.2 (7.9-28.5) | 10.6 (6.8-14.4) |
| 15 years after first breast cancer | 40.8 (33.2-48.3) | 20.9 (9.7-32.1) | 15.3 (10.4-20.3) |
| 25 years after first breast cancer | 55.1 (45.4-64.9) | 38.4 (18.5-58.2) | 28.4 (20.5-36.3) |
| Age at first breast cancer 40-49 years | | | |
| 5 years after first breast cancer | 9.2 (5.8-12.5) | 6.9 (2.7-11.1) | 4.2 (2.9-5.5) |
| 10 years after first breast cancer | 16.7 (11.7-21.7) | 13.4 (7.0-19.8) | 8.4 (6.3-10.5) |
| 15 years after first breast cancer | 23.2 (16.9-29.6) | 22.0 (12.1-31.9) | 10.7 (8.1-13.3) |
| 25 years after first breast cancer | 44.5 (33.2-55.7) | 40.5 (22.4-58.6) | 18.1 (13.9-22.3) |
| Age at first breast cancer ≥ 50 years | | | |
| 5 years after first breast cancer | 7.1 (3.8-10.5) | 3.5 (0.9-6.1) | 3.6 (2.7-4.5) |
| 10 years after first breast cancer | 11.4 (6.5-16.3) | 10.4 (4.9-16.0) | 5.5 (4.3-6.7) |
| 15 years after first breast cancer | 18.7 (11.0-26.3) | 15.5 (7.8-23.3) | 8.1 (6.3-9.9) |
| 25 years after first breast cancer | 21.6 (12.3-30.8) | 15.5 (7.8-23.3) | 12.9 (8.9-17.0) |
| Total | | | |
| 5 years after first breast cancer | 10.4 (8.3-12.5) | 4.5 (2.5-6.5) | 3.9 (3.2-4.6) |
| 10 years after first breast cancer | 20.4 (17.1-23.7) | 13.2 (9.2-17.2) | 7.1 (6.0-8.2) |
| 15 years after first breast cancer | 28.7 (24.4-32.9) | 19.0 (13.5-24.4) | 9.9 (8.5-11.4) |
| 25 years after first breast cancer | 44.1 (37.6-50.6) | 33.5 (22.4-44.7) | 17.2 (14.5-19.9) |

Therapy of BRCA1/2-associated Breast Cancer+

Limited prospective cohort studies with short follow-up time

| | Oxford / AGO LoE / GR | | |
|---|--------------------------|---|------|
| ➤ Breast conserving therapy: | | | |
| ➤ Adequate local tumor control (10 years observation) | 2a | B | + |
| ➤ Systemic therapy according to sporadic breast cancer | 3a | B | + |
| ➤ BRCA1 mutation status is predictive for chemotherapy response | 3b | B | + |
| ➤ Platinum-based regimens | 3 | B | +/-* |
| ➤ PARP inhibitor in breast cancer | 2b | D | +/-* |

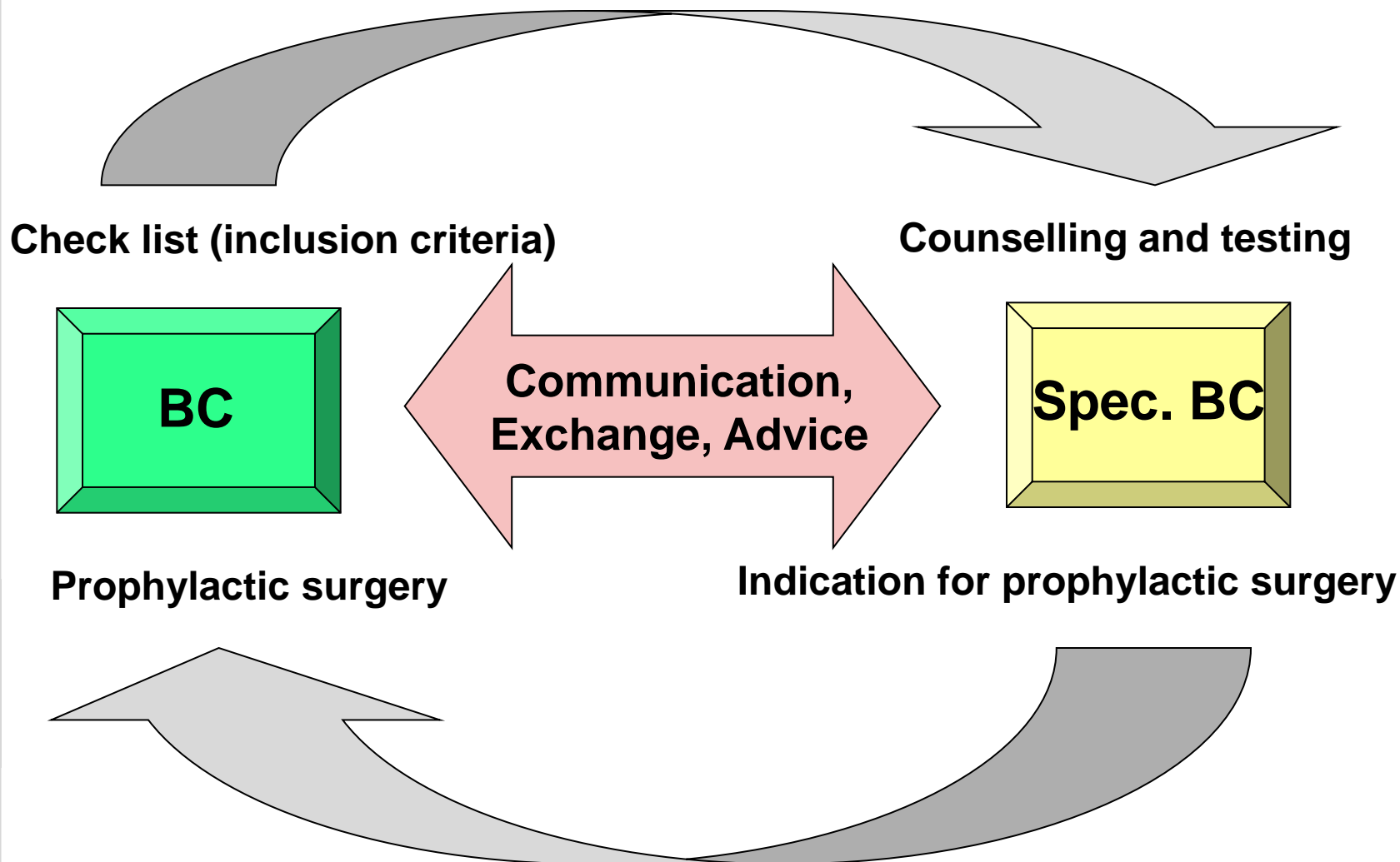
+ Overall prognosis has to be considered

*Study participation recommended

Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC

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Medical Prevention for Women at Increased Risk

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- **Tamoxifen for women > 35 years**
Reduction of invasive BrCA, DCIS, and LN
- **Raloxifen for postmenopausal women**
Reduction of invasive BrCa only
- **AI for postmenopausal women**

1a A +*

1b A +*

1b A +[#]

#Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers
Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

***Risk situation as defined in NSABP P1-trial (1.66% in 5 years)**

Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

**Oxford / AGO
LoE / GR**

| | | | |
|---|-----------|----------|----------|
| ➤ Tamoxifen* | 1a | A | + |
| ➤ Aromatase inhibitors* | 1a | A | + |
| ➤ Suppression of ovarian function* + Tamoxifen | 1b | B | + |

***Only proven for ER/PgR-positive primary sporadic BrCa**

Further
Information

References

Breast Cancer Risk and Prevention (2/29)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references

Principles in Prevention (3/29)

No further information

No references

Who Should be Tested for BRCA1/2 Mutations? (4/29)

No further information

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2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of up-dated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%.

Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013 (5/29)

No further information

No references

Use of a Screening Checklist (6/29)

No further information

References:

www.aekwl.de/brustzentren-download

Variants of Unknown Significance (VUS): 5-30% of all BRCA1/2 Mutations Detected (7/29)

No further information

References:

Plon et al., Human Mutation, 2008
e.g. Guidugli et al. 2013

VUS: Problems and Questions (8/29)

No further information

No references

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No further information

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No further information

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2. Tan et al., Lifetime cancer risks in individuals with germline PTEN mutations, *Clin Cancer Res.* 2012 Jan 15;18(2):400-7
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4. Hearle et al., Frequency and Spectrum of Cancers in the Peutz-Jeghers Syndrome, *Clin Cancer Res* May 15, 2006, 12; 3209
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Third Moderate to High Risk Gene Identified within the GC-HBOC (11/29)

No further information

References:

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Available, non-validated Breast Cancer Gene Panels for Risk Prediction (12/29)

No further information

References:

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2. Rare Mutations in XRCC2 Increase the Risk of Breast Cancer. Park DJ, Lesueur F, Nguyen-Dumont T, Pertesi M, Odefrey F, Hammet F et al. (2012) Am J Hum Genet. 90:734-739.

Low Risk Variants from Genome Wide Association Studies (GWAS) (13/29)

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1. Genome-wide association study identifies novel breast cancer susceptibility loci (2007). Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG et al. Nature. 447: 1087-93
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Low Risk Variants as Modifier (14/29)

No further information

Low Risk Variants as Modifiers (retrospective)

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Genetically Defined Subtypes are Distinct Tumor Entities (15/29)

No further information

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Current Clinical Impact of Other Risk Genes (16/29)

No further information

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Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (17/29)

No further information

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http://www.bmg.bund.de/fileadmin/dateien/Downloads/N/Nationaler_Krebsplan/Zielepapier_zum_Querschnittsthema_Risikoadaptierte_Krebsfrueherkennung.pdf

Non Directive Counseling for the Uptake of Preventive Measures (18/29)

No further information

No references

Definition of Women at Moderate to High Risk (19/29)

No further information

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Surveillance Program for Women with deleterious BRCA-mutations (20/29)

Further information:

The German Consortium for Hereditary Breast and Ovarian Cancer has established an intensive surveillance program that is offered to mutation carriers and women at high risk within the 12 centres of familial breast and ovarian cancer in Germany (Meindl A, Ditsch N, Kast K, Rhiem K, Schmutzler RK Hereditary breast and ovarian cancer: new genes, new treatments, new concepts. Dtsch Arztebl Int. 2011 May;108(19):323-30. doi: 10.3238/arztebl.2011.0323. Epub 2011 May 13.

These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).

The surveillance program allows the detection of early stage breast carcinomas (MARIBS study group Lancet 2005, Kriege et al. NEJM 2004, Warner et al. JAMA 2004, Kuhl, Schmutzler et al. 2000). However, no data exist so far on long term follow-up and mortality reduction.

BRCA associated breast carcinomas frequently present with specific imaging criteria that may be misinterpreted as benign lesions by sonography and mammography (Rhiem K et al. Am J. Roentgenology 2006, Tilanus-Linthorst M et al. Int J Cancer 2002, Kaas R et al. Eur Radiol 2004, Hamilton LJ Clin Radiol 2004)

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Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease (21/29)

No further information

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Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (22/29)

Further information:

Prophylactic bilateral salpingo-oophorectomy (PBSO) reduces the risk for ovarian cancer in BRCA1/2 mutation carriers to >95% and the risk for breast cancer to 50% (Kauff et al. NEJM 2002, Rebbeck et al. NEJM 2002). Short term HRT does not negate the protective effect of PBSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, PBSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend PBSO in mutation carriers after completion of childbearing around the age of 40.

Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.

For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).

The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be preceded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)

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8. Domcheck et al. 2010
9. Sitzmann et al., JAMA Surg 2013

Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (23/29)

No further information

References:

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Domchek SM, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C et al. Association of risk reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA* (2010) 304:967-75.

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Metcalfe K, Lynch HT, Ghadirian P, et al: Contra-lateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 22: 2328-2335, 2004

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Risk-reducing Salpingo-oophorectomy and All-cause Mortality (24/29)

No further information

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Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive) (25/29)

No further information

No references

Therapy of BRCA1/2-associated Breast Cancer+ (26/29)

No further information

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Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (27/29)

No further information

No references

Medical Prevention for Women at Increased Risk (28/29)

No further information

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Risk Reduction for Ipsi- and Contralateral Breast Cancer (29/29)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Early Detection and Diagnosis

Early Detection and Diagnosis

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➤ Versions 2005–2013:

**Albert / Blohmer / Fersis /
Junkermann / Maass / Scharl /
Schreer**

➤ Version 2014:

Schreer / Blohmer

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Further
Information

References

Early Detection Mammography

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| Age | Interval | Oxford | | AGO |
|--------|----------|--------|----|-----|
| | | LOE / | GR | |
| < 40 | na | - | - | -- |
| 40–50 | 12–18 | 1b | B | + |
| 50–70* | 24 | 1a | A | ++ |
| >70 | 24 | 4 | C | + |

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Further
Information

References

* National Mammography-Screening-Program

Breast Cancer Mortality Reduction

Metaanalyses

RR 95%CI

Independent UK Panel, 2012

13-year metaanalysis

0.80 (0.73–0.89)

Cochrane Review, 2011

Fixed-effect metaanalysis of 9 RCT-trials

0.81 (0.74–0.87)

As above, but excluding women <50 years

0.77 (0.69–0.86)

US Task Force, 2009

Women 50–59 years

0.86 (0.75–0.99)

Women 60–69 years

0.68 (0.54–0.87)

Estimates weighted average

0.81

Canadian Task Force, 2011

Women aged 50–69 years

0.79 (0.68–0.90)

Duffy et al., 2012

Review of all trials and age groups

0.79 (0.73–0.86)

Mammography-Screening

Women 40–49 Years

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RR (invited women)

0.74 (95%CI 0.66-0.83)

40–44 J

0.83 (95%CI 0.67-1.00)

45–49 J

0.68 (95%CI 0.59-0.78)

Participants

0.71 (95%CI 0.62-0.80)

NNS

1252 (95%CI 958-1915)

(1 live saved / 10 years screening)

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Information

References

Early Detection Sonography

Oxford / AGO
LOE / GR

- **Screening-Breast Sonography**
 - **Automated 3D-Sonography**

5 D - -
3b C - -

As an adjunct:

- **Dense mammogram (ACR 3– 4)**
 - **Elevated risk**

2b B ++
1b C ++

- **Mammographic lesion**

2b B ++

- **Second-look US (MRI-only detected lesions)**

2b C ++

Early Detection Clinical Examination

**Oxford / AGO
LOE / GR**

As stand alone procedure

- | | | | |
|--|-----------|----------|-----------|
| ➤ Self-examination | 1a | A | -* |
| ➤ Clinical breast examination (CBE) by health professionals | 3b | C | -* |
| ➤ CBE because of mammo/sonographic lesion | 5 | D | ++ |

CBE in combination with imaging

BCP **++**

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Further
Information

References

**FORSCHEN
LEHREN
HEILEN**

* May increase breast awareness

Assessment of Breast Symptoms or Lesions

Oxford / AGO LOE / GR

| | | | |
|------------------------------------|-----------|----------|------------|
| ➤ Clinical examination | 3b | B | ++ |
| ➤ Mammography | 1b | A | ++ |
| ➤ Tomosynthesis | 3b | C | +/- |
| ➤ Sonography | 2b | B | ++ |
| ➤ Elastography (shear-wave) | 3b | C | + |
| ➤ Automated 3D-sonography | 3b | C | +/- |
| ➤ MRI* | 2b | D | +/- |
| ➤ Minimally invasive biopsy | 1c | A | ++ |

* If clinical examination, mammography and sonography do not allow a definite diagnosis

Pretherapeutic Assessment of Lesion Extension and Staging

| | Oxford LOE | / GR | AGO |
|--------------------------------------|---------------|----------|------------|
| ➤ Clinical examination | 5 | D | ++ |
| ➤ Mammography | 2b | B | ++ |
| ➤ Sonography | 2b | B | ++ |
| Axilla + FNP/CNB | 2b | B | + |
| ➤ MRI * | 1b | B | +/- |
| ➤ Minimally invasive biopsy** | 1b | A | ++ |

* Weak reduction in reexcision rate in lobular- invasive cancer but sign. higher rate of initial mastectomy. Lobular invasive tumors, suspicion of multilocular disease, high-risk patients. MRI-guided vacuum biopsy mandatory in case of MRI-detected additional lesions.

** If clinical examination, mammography and sonography (e.g. plus MRI) do not allow assessment of lesion extension

MRI: Preoperative Staging?

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| | |
|---|-------------------|
| False negative rate | 4–12 % |
| False positive rate | up to 40 % |
| No fewer positive margins | |
| Odds ratio for mastectomy | 1.80 |
| Delay in pretreatment evaluation | 22.4 days |

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Further
Information

References

J Bleicher et al J Am Coll Surg 2009; 209

MRI: Preoperative Staging

- **9 eligible studies (2 randomized trials;
7 comparative cohorts)**
- **3112 patients with BC**
- **MRI versus no-MRI:**
 - **initial mastectomy 16.4% versus 8.1% [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]**
 - **re-excision after initial breast conservation 11.6% versus 11.4% [OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P = 0.71)]**
 - **overall mastectomy 25.5% versus 18.2% [OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]**

N Houssami et al. Ann Surg 2013; 257

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

- **766 patients with invasive lobular cancer (ILC)**
 - **initial mastectomy: 31.1% versus 24.9% [OR, 1.36 (P = 0.056); adjusted OR, 2.12 (P = 0.008)]**
 - **re-excision after initial breast conservation 10.9% versus 18.0% [OR, 0.56 (P = 0.031); adjusted OR, 0.56 (P = 0.09)]**
 - **overall mastectomy 43.0% versus 40.2% [OR, 1.12 (P = 0.45); adjusted OR, 1.64 (P = 0.034)]**

N Houssami et al. Ann Surg 2013; 257

COMICE Trial (RCT)

MRI preop. vs. no preop. MRI

Results

816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0.96, 95% CI 0.75–1.24; $p=0.77$).

Conclusion

- No significant reduction of reoperation rate
- More costs with low or no benefit

L Turnbull et al. Lancet 2010

MONET Trial (RCT)

Routine-Care vs. Preoperative MRI

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| | Positive Margin | Addition Surgery |
|------------------|-----------------|---------------------|
| Routine-Care | 12% | 28% |
| Preoperative MRI | 34% | 45% |

„Breast MRI should not be used routinely for preoperative work-up of patients with non-palpable breast cancer.“

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Further
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References

MRI Scceening (High-risk) Benefit

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- **Early detection of cancer cases additionally to conventional imaging**
- **Improved patient prognosis?
(Mortality reduction? Reduction of interval cancers?)**

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MRI Screening (High-risk) Problems

**MRI in addition to
mammography**

RR

**Assessment of benign
lesions**

3,43–4,86

Benign biopsies

1,22–9,50

**Benign surgical biopsies
(MARIBS)**

2

False-negative MRI (MRISC)

22%

False-negative MRI in High-risk Women (MRISC)

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- **97 malignant breast tumors**
19 /97 (20%) DCIS
- **21 /97 (22%) false-negative**
9 /21 (20%) DCIS

**„.....Necessity of screening not only with
MRI but also with mammography.“**

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Information

References

Obdeijn IMA et al. 2010

MRI and DCIS

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| Study | No. Cases | Overall accuracy (%) | Sens. (%) | Spec. (%) |
|-------------------------|--------------|-------------------------|--------------|-----------|
| Gilles et al 1995 | 172 | 70 | 95 | 51 |
| Westerhof et al 1998 | 63 | 56 | 45 | 72 |
| Bazzocchi et al 2006 | 112 | 80 | 79 | 68 |
| Kuhl et al 2007 | 75 | - | 88 | - |
| Baur et al 2013 | 58 | - | 79,3 | |

„Negative breast MRI findings should not be considered a sure marker of benignancy.“

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Further
Information

References

Early Detection and Diagnosis (2/18)

Further information:

Screened data bases:

- Pubmed 2009 - 2013
- ASCO 2009 - 2013
- Cochrane 2009 - 2013
- Medline 2009 - 2013
- GIN 2009 - 2013

Guidelines

- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge

Screened: Metaanalysen / systematische Reviews / RCT / Beobachtungs-und Fallkontrollstudien

No references

Early Detection – Mammography (3/18)

Further information:

The aim of early detection and screening of breast cancer is to reduce the risk of dying from the disease. Detecting invasive breast cancer at an early stage (Stage I-IIA) offers the chance of survival with less treatment impairment and better quality of life.

Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false positives, false negatives, overdiagnosis and overtreatment.

Since 2006 mammography screening is offered to women age 50-69 in Germany within a population-based organized quality assured programme in accordance with the European Guidelines for Quality Assurance in Mammography Screening.

Meta-analysis and reviews from randomised trials:

Conclusion of the meta-analysis of the Independent UK Panel on Breast Cancer Screening: “Considering the internal bias in the trials, which were done a long time ago, the relative risk reduction in breast cancer mortality from invitation to mammography screening is estimated to be 20%.”

The updated modelling of Forrest report (QUALYs after 7,10 and 20 years) concludes “the introduction of breast cancer screening might have caused net harm for up to 10 years after start of screening”.

Data from observational studies and registries:

The EUROCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: 1. “the best “European” estimate of of breast cancer reduction is 25-31% for women invited for screening, and 28-38% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis.

The population-based data from the United States (SEER-Cancer Statistics 1976 - 2008) showed an increase in number of early-stage breast cancer, a marginal reduction at advanced stage. The authors conclude “the imbalance suggests that there is substantial overdiagnosis, and that screening at best, only has a small effect on the rate of death from breast cancer”.

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Breast Cancer Mortality Reduction (4/18)

No further information

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Mammography Screening Women 40–49 years (5/18)

Further information:

On the basis of randomized controlled trials there is evidence of a 26% mortality reduction. The only one especially designed for this age group (“Age-Trial”) achieved a mortality reduction of 17% for those invited and 24% for those participating. These results were not yet statistically significant (95% CI, 0.66-1.04)), because the follow-up time is too short for this young age group. The data have been underlined by study results of several service screening studies. The most recent one (Hellquist and coauthors 2011) presented a 26% mortality reduction in those invited and 29% in those attending. The average follow-up time was 16 years.

To estimate overdiagnosis within the “Age-Trial” Markov-modelling was performed and yielded the following results (Gunsoy N, 2012): “The sensitivity of mammography for invasive and in-situ breast cancers was 90% (95% CI, 72-99) and 82% (43-99), respectively. The screen-detectable mean sojourn time of preclinical non-progressive and progressive in-situ cancers was 1.3 (0.4-3.4) and 0.11 (0.05-0.19) years, respectively, and 0.8 years (0.6-1.2) for preclinical invasive breast cancer. The proportion of screen-detected in-situ cancers that were non-progressive was 55% (25-77) for the first and 40% (22-60) for subsequent screens. In our main analysis, overdiagnosis was estimated as 0.7% of screen-detected cancers. A sensitivity analysis, covering a wide range of alternative scenarios, yielded a range of 0.5% to 2.9%.” The authors conclude: “The extent of overdiagnosis due to screening in women aged 40-49 was small. Results also suggest annual screening is most suitable for women aged 40-49 in the United Kingdom due to short cancer sojourn times.”

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Early Detection Sonography (6/18)

Further information:

Results from the systematic review (Nothacker et al): The systematic search identified no randomized controlled trials or systematic reviews, six cohort studies of intermediate level of evidence (3b) were found. Only two of the studies included adequate follow-up of subjects with negative or benign findings. Supplemental breast ultrasound after negative mammographic screening permitted diagnosis of primarily invasive carcinomas in 0.32% of women in breast density type categories 2-4 of the American College of Radiology (ACR); mean tumor size for those identified was 9.9 mm, 90% with negative lymph node status. Most detected cancers occurred in mammographically dense breast ACR types 3 and 4. Biopsy rates were in the range 2.3%-4.7%, with PPV of 8.4-13.7% for those biopsied due to positive ultrasound, or about one third of the PPV of biopsies due to mammography. Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permits detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group are associated with an increased biopsy rate.

The arguments against ultrasound use as a screening modality alone are reproducibility, high false-positive rate, low ppv for biopsy, inability to detect most DCIS cases, operator dependency and lack of quality assurance.

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Early Detection Clinical Examination (7/18)

Further information:

In a large well performed randomized study no difference in breast cancer mortality emerged after 11 years of follow-up. The only difference was that women in the self-examination arm had nearly twice as many biopsies for benign lesions than women in the control arm. Therefore based on current evidence breast self-examination cannot be recommended anymore. No randomized studies have been performed, where screening-examination by health professionals is compared to no screening. One Japanese case-control study suggests that examination by health professionals might reduce mortality from breast cancer. A randomized trial in Canada showed no difference in breast cancer mortality between a group of women offered clinical breast examination or mammography combined with clinical breast examination. Nevertheless in asymptomatic women participating in mammography screening programs there is the risk of interval cancer development. This is the reason why in the US mammography screening is recommended in close connection with clinical examination. Recent data (Haakinson and coauthors 2010) underscore this strategy.

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Assessment of Breast Symptoms or Lesions (8/18)

Further information:

If clinical examination, mammography and ultrasound are not conclusive, morphological diagnosis based on biopsy material is warranted. MRI has a high sensitivity but a low specificity to allow definitive diagnosis.

Minimally invasive biopsy allows definitive diagnosis in most cases at reduced expenditure.

In case of suspicious microcalcifications extensively distributed in mammography several percutaneous biopsies should be performed before deciding upon mastectomy.

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Pretherapeutic Assessment of Lesion Extension (9/18)

Further information:

Sonography corresponds better than mammography with the pathological tumor size of the invasive component of breast tumours. Mammography delineates the in situ component better if microcalcifications are present. In these cases magnification mammography is warranted. MRI is the most sensitive method for invasive tumors, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment. The effect of MRI on the success of breast conserving therapy neither concerning short-time outcome parameter, i.e. reduction of re-excision rate nor longtime outcome parameter, i.e ipsilateral recurrence and overall survival have not been assessed in randomized studies. Therefore the overall contribution of MRI to successful breast conserving therapy cannot be assessed yet. MRI for preoperative staging may be helpful in individual cases (high-risk women, multifocality/ multicentricity demonstrated at conventional imaging and pathologically proven, invasive lobular cancer with inconclusive findings at conventional imaging).

In case of large areas of highly suspicious microcalcifications on mammography several percutaneous biopsies to define tumour size should be performed before deciding upon mastectomy.

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MRI Preoperative Staging? (10/18)

No further information

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MRI Preoperative Staging (11/18)

No further information

No references

MRI Preoperative Staging in Lobular Invasive Breast Cancer (12/18)

No further information

No references

COMICE Trial (RCT): MRI preop. vs. no preop. MRI (13/18)

No further information

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MONET Trial (RCT) (14/18)

No further information

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MRI Scceening (High-risk) Benefit (15/18)

No further information

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MRI Scening (High-risk) Problems (16/18)

No further information

References:

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False-negative MRI in High-risk Women (MRISC) (17/18)

No further information

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1. Obdeijn IMA, Loo CE, Rijnsburger AJ, Wasser MNJ, Bergers E, Kok T, Klijn JGM, Boetes C Assessment of false-negative cases of breast MR imaging in women with a familiar or genetic disposition. Breast Cancer Res Treat 2010; 119: 399-407

MRI and DCIS (18/18)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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FORSCHEN
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Handling and Reporting of Core Needle Biopsies

Oxford / AGO
LoE /GR

- **Routine workup in step sections
(14G: 3 sections / 11G, 8G: 6–8 sections)**
- **Correlation with imaging (density,
calcifications), use of B-Classification**
- **Frozen section diagnosis on core biopsies**
- **Routine evaluation of ER/PgR and HER2
status**
- **Turn-around time < 24 h (dignity)**
- **Optimal fixation time 6–48 h**
- **Standard fixation and processing**
- **Participation in QA-programs**

5 D ++

1b B ++

5 D - -

3b C ++

5 D +

5 D ++

5 D ++

3 D ++

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Fine Needle Aspiration Cytology*

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- **Nipple secretion**
- **Tumor**
- **Cyst**
- **Lymph node**

| Oxford / LoE / GR | AGO |
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*** Ultrasound-guided core biopsy recommended**

Indications for Immediate Pathological Analysis Including Frozen Sections

| | Oxford / AGO LoE /GR | | |
|--|-------------------------|---|-----|
| ➤ Sentinel node biopsy for invasive cancer | | | |
| - if clinical consequence | 5 | D | + |
| - if no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET) | 5 | D | +/- |
| ➤ Closest margin of resection | | | |
| - if macroscopically < 1 cm | 5 | D | + |
| - if macroscopically > 1 cm | 5 | D | - |
| ➤ Lesions ≥ 1 cm, without core biopsy | 5 | D | + |
| ➤ Non-palpable lesions or lesions < 1 cm | 5 | D | -- |
| ➤ Asservation of fresh tissue (tumor banking) | 5 | D | + |

General Recommendations for Specimen Handling

Oxford / AGO
LoE / GR

- | | | | |
|--|---|---|----|
| ➤ Adherence to sampling protocols and guidelines for accurate evaluation of tumor size and margins | 5 | D | ++ |
| ➤ Consideration of clinical imaging results (e.g. calcifications, multifocality) and topography | 5 | D | ++ |
| ➤ Specimen radiography for non-palpable lesions and microcalcifications | 5 | D | + |
| ➤ Minimum fixation time 6 h (max. 48 h) to minimize shrinking artifacts and allow determination of angioinvasion | 5 | D | + |
| ➤ Tissue banking to be performed by or in cooperation with the pathologist | 5 | D | + |

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Workup of Breast-Conserving Specimens

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|-----------|
| ➤ Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens) | 5 | D | ++ |
| ➤ Systematic sampling, at least 1 tissue block every 1 cm | 5 | D | ++ |
| ➤ Inking of resection margins. Sampling of resection margins in all dimensions | 5 | D | ++ |
| ➤ Documentation after slicing using specimen radiography, photodocumentation or diagram | 5 | D | + |

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Workup of Mastectomy Specimens

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- **Margins always to be sampled**
 - skin close to tumor, at least 2 directions
 - deep margin
 - other margins, if close (< 1 cm)
- **Attention to soft tissue margins in skin sparing mastectomy**
- **Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region**
- **More extensive sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)**

**Oxford / AGO
LoE /GR**

5 D ++

5 D ++

5 D ++

5 D ++

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Reporting of Invasive Carcinoma

Oxford / AGO
LoE / GR

- | | | | |
|---|-----------|----------|-----------|
| ➤ Tumor type (WHO). Grade (UICC). Size (invasive and extensive in situ cancer). pT classification (UICC). | 3b | C | ++ |
| ➤ All margins, macroscopically, distance and topography. Histologic distance and topography of margins < 1 cm. R-Classification according to TNM. | 3b | C | ++ |
| ➤ EIC (if present). Multifocality (if present). Lymphovascular invasion (present or not). | 5 | D | ++ |
| ➤ No. of axillary nodes removed. No. and size of lymph node metastases. Perinodal invasion. pN classification (UICC). | 3b | B | ++ |
| ➤ ER, PgR, HER2 status | 3b | C | ++ |
| ➤ Ki-67 (for re-assurance of grading) | 3b | B | + |

Evaluation after Neoadjuvant Chemotherapy

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| | Oxford LoE / GR | / | AGO GR |
|--|--------------------|---|-----------|
| ➤ Identification of tumor bed, otherwise ypTX | 4 | D | ++ |
| ➤ Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma | 4 | D | ++ |
| ➤ Reporting of tumor regression according to Miller-Payne (2003), Symmans (2007) or Sinn (1994), Sataloff or Chevallier (1993) | 4 | D | + |
| ➤ pCR when absence of invasive and in situ Ca. and absence of vessel invasion or LN metastases | 2b | D | + |
| ➤ Use of IHC to identify tumor residues | 4 | D | +/- |
| ➤ Final reporting pTN before and after therapy | 5 | D | ++ |

Histologic Evaluation of Tumor Regression

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- **NSABP B-18:** pCR / pPR / NR
- **Chevallier:** Grade of regression, 1–4
- **Sataloff:** Cellularity (Tu + Lnn), 1–4
- **Miller-Payne:** Cellularity, Score 0–5
- **Symmans:** 6 parameter (Tu + Lnn)
- **Sinn:** Grade of regression, Score 0–4

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Definition of pCR

| Author Grades of regr. | Invasive tumor | In-situ tumor | Intra- vascular | Lymph-node metas. |
|--|-------------------|------------------|--------------------|----------------------|
| Chevallier 1–4 | - | - | - | - |
| Sinn 0-4 | - | - | - | +/- |
| Sataloff Cellularity 1–4 | -/+ | -/+ | -/+ | - |
| Miller-Payne Cellularity 1–5 | - | -/+ | - | - |
| Symmans 6 parameters | - | - | - | - |
| NSABP B-18 pCR / pPR / NR | - | -/+ | - | - |
| GBG / AGO-B | - | - | - | - |

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ER, PgR Testing

Oxford / AGO
LoE / GR

- | | | | |
|--|----|---|----|
| ➤ Immunohistochemical detection on paraffin embedded (FFPE) tissue | 1a | A | ++ |
| ➤ Reporting percentage of pos. tumor nuclei (pos. if $\geq 1\%$) | 1a | A | ++ |
| ➤ Staining intensity of pos. tumor nuclei | 4 | D | + |
| ➤ Quantitative RNA assessment (qt-pCR, array) | 2b | B | - |
| ➤ Allred Score (0–8), Remmele Score (0–12) | 4 | D | + |
| ➤ Re-evaluation on excision specimen if triple-negative on core biopsy | 5 | D | + |
| ➤ Use of internal and external quality control schemes | 5 | D | ++ |

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ER/PgR Interpretation

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| Klassifikation | ASCO/CAP 2010 | Remmele-Score | Allred-Score | St Gallen Konsensus 2009 |
|--|------------------|---|--|-----------------------------|
| Bewertung | Prozentualität | Färbeintensität (1-3)x Prozentualität (1-4) = max. 12 | Färbeintensität (1-3)+ Prozentualität (1-5) = max. 8 | Prozentualität |
| | | > 0 bis < 10% = 1 | > 0 bis 1% = 1 | Schwach positiv: >0-49% |
| | | 10 bis < 50% = 2 | > 1% bis 10% = 2 | |
| | | 50% bis 80% = 3 | > 10% bis 33% = 3 | Hoch positiv: = 50% |
| | | > 80% = 4 | > 33% bis 66% = 4 | |
| | | | > 66% bis 100% = 5 | |
| Positiv | Positiv = 1% | Positiv = 3 (Score) | Positiv = 3 (Score) 1% mäßig gefärbt | Positiv > 0 (%) |
| Negativ | Negativ < 1% | Negativ = 2 (Score) | Negativ = 2 (Score) | Negativ 0 (%) |
| Diskrepante Positivitäts- Grenze im Vergleich zu ASCO/CAP | | 1% mindestens stark gefärbt | 1% mindestens mäßig gefärbt | >0% - <1% |
| Diskrepante Negativitäts- Grenze im Vergleich zu ASCO/CAP | | 49% schwach gefärbt; 9% mäßig gefärbt | 1% schwach gefärbt | >0% - <1% |

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HER2 Testing

Oxford / AGO
LoE / GR

1a A ++

- **Reporting of immunohistochemistry (IHC):**
 - HER2+ if strong complete circular membrane staining of >10% invasive cells (3+ staining pattern)
 - if > 10% circular but moderate/weak membrane staining or ≤10% strong staining (2+ staining pattern): ISH required (CISH, SISH, FISH)

3a C ++

- **Reporting of single-color In-Situ-Hybridisation (ISH):**
 - HER2+ if signal counts ≥6 in at least 20 cohesive cells, negative if signal counts < 4 signals/nucleus

3a C ++

- **Reporting of dual-color ISH:**
 - positive if signal ratio HER2:CEP17 ≥ 2,0 and/or HER2-signals ≥6

3a C ++

- **Equivocal results (2+ IHC, ≥4 - <6 HER2 signals ISH): Retest using other method and/or tissue block**

5 D ++

- **Validation of immunohistochemistry on core biopsies**

5 D ++

- **Use of internal and external quality control schemes**

2b B --

- **Reporting by RNA-analysis (qtPCR, array-technology)**

HER2 Testing on Core Biopsies

False positive immunohistochemical labeling may occur in core biopsies.

Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium.

Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.

False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PgR positive, Tubular (at least 90% pure), Mucinous (at least 90% pure) Cribriform (at least 90% pure), Adenoid cystic carcinoma (90% pure)

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples.

Expected rate of HER2-overexpression: 15% HER2 positive

Intrinsic Breast Cancer Types

(Molecular and Immunohistochemical Definitions)

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- **Currently there is no generally accepted and proven translation of molecularly defined types (basal, luminal A/B-Typ, HER2) into immunohistochemical counterparts neither with regard to markers nor to thresholds**
- **In terms of practical consequences re-labelling of clinically established and immunohistochemically defined subgroups might be useful (ER/PR+ for luminal, HER2+ for HER2-type, triple negative for basal type)**
- **The basal type shows an 80% overlap with the triple negative subgroup of ductal invasive breast cancer (ER <1% & PgR <1% & HER2 0/1+2+ (non-amplified, ratio <2))**
- **None of the available markers (Ki-67, grading, recurrence score etc.) can reliably discriminate between luminal A and luminal B type**
- **Although derived from RNA expression studies, RNA measurements are not suited for the definition of intrinsic types for purposes of therapy**

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Triple-negative Breast Cancer (TNBC)

Oxford LoE: 5

GR: D

AGO: ++

- **Definition: ER <1% & PgR <1% & HER2 0/1+2+ (not amplified, Ratio ≤ 2)**
- **Except: Salivary gland type tumors, myoepithelial Ca., adenoid-cystic Ca., apocrine Ca.**
- **Repeat IHC if equivocal result***

*** Equivocal result: tubular, lobular, mucinous, cribriform breast ca., slowly proliferating IDC G2, possible sampling bias (core biopsy), negative for basal cytokeratins**

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Evaluation of Sentinel Node Biopsy

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- Full workup using step sections of
≤ 500 µm on paraffin embedded tissue
- Cytokeratin immunohistochemistry
 - when suspicious, to detect micromet.
 - as a routine procedure
- Frozen section (invasive Ca.)
 - if clinical consequence
 - if no clinical consequence from frozen section
(e.g. cT1 or cT2 and cN0 and BET)
- Imprint cytology instead or in addition of frozen
section
- RT-PCR for epithelial genes
 - OSNA

Oxford / AGO
LoE / GR

5 D ++

2b B ++
5 D +/-

5 D +
5 D +/-

3b C +/-

4 D -
3b B -

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Mutation or Expression Analysis

Oxford LoE: 5

GR: D

AGO: - -

- **TP53 (p53)**
- **PIK3CA (PI3K)**
- **PTEN**
- **Others**

- **Whole genome sequencing**

- **Currently, only for scientific use!**

Pathology (2/20)

Further information:

This chapter contains basic recommendations for routine procedures in pathology. It is not attempted to replace detailed protocols for the evaluation of operative specimens or for special studies. It is highly recommended to adhere to national quality assurance protocols concerning all aspects of working up and reporting of pathology specimens removed from women with breast cancer. Further information can be found in the following reports:

Update 1/2014 –Kreipe / Friedrichs

Screened data bases: PubMed 1970 – 2013

Screened guidelines:

- German S3-Guideline Early Detection of Breast Cancer
- German S3-Guideline Treatment of Breast Cancer (Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms)
- EUSOMA position paper: Diagnosis of breast disease
- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition

References:

1. Arbeitsgruppe Qualitätssicherung Pathologie in der konzertierten Aktion zur Brustkrebsfrüherkennung in Deutschland (2002). Anleitung Mammapathologie. Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 2008.
http://www.senologie.org/download/pdf/s3_brustkrebsfrueherkennung_2008.pdf
2. Association of Directors of Anatomic and Surgical Pathology (1996). Recommendations for the reporting of breast carcinoma. Mod Pathol. 1996 Jan;9(1):77-81.

3. Deutsche Krebsgesellschaft und beteiligte medizinisch-wissenschaftliche Fachgesellschaften (2008). Interdisziplinäre Leitlinie Diagnose und Therapie des Mammakarzinoms der Frau. http://www.senologie.org/download/pdf/s3_ll_mammaca_11_02_2008.pdf
4. Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, Hayes DF, Kleer C, O'Malley FP, Page DL, Smith BL, Tan LK, Weaver DL, Winer E; Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009 Oct;133(10):1515-38.
5. Reiner-Concin, S. Lax. Mammakarzinom Pathologie. In: Manual der gynäkologischen Onkologie. Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) A. Reinthaller, L. Hefler (Hrsg.) <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>
6. Schweizerische Gesellschaft für Pathologie (2002). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. <http://www.sgpath.ch>
7. Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006
8. Royal College of Pathologists (UK) (2005). NHSBSP guidelines for pathology reporting in breast disease. <http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html>
9. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8

Handling and Reporting of Core Needle Biopsies (3/20)

Further information and references:

Statement: Routine workup in step sections

Routine workup of core needle biopsies is in step sections (14G: 3 sections / 11G, 8G: 6 – 8 sections). In general, ultrasound guided core biopsies (14G) are performed for mass lesions. It is recommended to cut only three routine sections to save tumor tissue for IHC and other studies. If in doubt, further sections should be cut. Vacuum cores (11G, 8G) are often used for non-palpable lesions and may include microcalcifications and/or B3 lesions. 6-8 step sections are required for adequate workup using H&E sections.

1. Krainick-Strobel U, Hahn M, Duda VF, Paepke S, Peisker U, Petrich S, Scheler P, Schwarz-Bocker U, Sinn HP, Heywang-Kobrunner S, Schreer I. Consensus recommendations for the application and indication of the vacuum biopsy of the breast under ultrasound view. Geburtshilfe Und Frauenheilkunde 65: 526-9, 2005
2. Heywang-Köbrunner SH, Sinnatamby R, Lebeau A, Lebrecht A, Britton PD, Schreer I; Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): results of a European consensus meeting. Eur J Radiol. 2009 Nov;72(2):289-94

Statement: Correlation with imaging

The B-Classification is recommended to improve reproducibility and to standardize treatment and follow up. The use of the B-Classification requires knowledge about the imaging results and, optimally, discussion with the radiologist in a conference.

1. Heywang-Köbrunner SH, Sinnatamby R, Lebeau A, Lebrecht A, Britton PD, Schreer I; Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): results of a European consensus meeting. Eur J Radiol. 2009 Nov;72(2):289-94

Statement: Frozen section diagnosis on core biopsies

Frozen tissue section of core biopsies is not recommended as a routine procedure and can be avoided by rapid tissue processing and reporting during daytime. Disadvantages of frozen section of core biopsies include: difficulties in interpretation, loss of relevant material, problems with immunohistochemistry.

1. Heywang-Köbrunner SH, Sinnatamby R, Lebeau A, Lebrecht A, Britton PD, Schreer I; Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): results of a European consensus meeting. Eur J Radiol. 2009 Nov;72(2):289-94

Statement: Routine evaluation of ER/PgR and HER-2 status

It is safe and preferred to routinely perform immunohistochemistry or other special studies on core biopsies provided adequate tumor tissue was biopsied. Advantages are: better preservation of tumor tissue, planning of inclusion into clinical studies such as neoadjuvant chemotherapy, more accurate assessment of tumor grading and tumor typing. In case of triple-negative or triple-positive tumors, evaluation should be repeated on excision specimen because of possible sampling error (tumor heterogeneity).

1. Harris G, Denley H, Pinder S et al. Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. Am J Surg Pathol 2003; 27: 11-15.
2. Chivukula M, Bhargava R, Brufsky A et al. Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. Mod Pathol 2008; 21: 363-368.
3. Wood B, Junckerstorff R, Sterrett G et al. A comparison of immunohistochemical staining for oestrogen receptor, progesterone receptor and HER-2 in breast core biopsies and subsequent excisions. Pathology 2007; 39: 391-395.

Statement: Turn-around time < 24h

Turn-around time until reporting should be one working day or less.

1. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006, pp 256-311

Statement: Cytology

Core needle biopsy has replaced fine-needle aspiration cytology, not only because it is more sensitive and specific, but also because it enables differentiation between invasive and in situ carcinomas in most cases.^{2,18–20} The introduction of CB has led to a reduction in surgery on benign lesions.

1. Andreu et al. Breast core biopsy reporting categories--An internal validation in a series of 3054 consecutive lesions. *Breast* (2007) vol. 16 (1) pp. 94-101
2. Ibrahim AE, Bateman AC, Theaker JM, et al. The role and histological classification of needle core biopsy in comparison with fine needle aspiration cytology in the preoperative assessment of impalpable breast lesions. *J Clin Pathol* 2001;54:121–5.

Statement: Fixation Time

Incisional and excisional biopsy samples used for HER2 testing of either type should be fixed in 10% neutral buffered formalin for intervals ranging from at least 6 hours to no more than 48 hours. Fixation time alters protein antigen expression and also changes the requirements for enzymatic digestion that is part of the ISH protocol to detect gene amplification. Prolonged fixation, for example more than 48 hours, may result in false-negative results. Fixation times for needle biopsies have not been addressed.

Statement: Standard fixation and processing

1. Wolff et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* (2007) vol. 131 (1) pp. 18-43
2. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31:3997-4013

Incisional and excisional biopsy samples used for HER2 testing of either type should be fixed in 10% neutral buffered formalin for intervals ranging from at least 6 hours to no more than 48 hours. Fixation time alters protein antigen expression and also changes the requirements for enzymatic digestion that is part of the ISH protocol to detect gene amplification. Prolonged fixation, for example more than 48 hours, may result in false-negative results. Fixation times for needle biopsies have not been addressed.

Statement: Participation in QA-programs

Systematic and effective use of diagnostic pathways is the basis for optimal treatment and the ability to substantially lower current breast cancer mortality rates and reduce the burden of this disease in the population. In order that benefits may be obtained, high-quality services are essential. These may be achieved through the underlying basic principles of training, specialisation, volume levels, multidisciplinary team working, the use of set targets and performance indicators and audit.

Quality assurance in surgical pathology is defined as a program for the systematic monitoring and evaluation of the various aspects of the laboratory service to ensure that standards of quality are being met. Quality improvement in surgical pathology is defined as a systematic attempt to improve specific quality measures in laboratory service.

1. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8
2. Perry et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Annals of Oncology (2008) vol. 19 (4) pp. 614-22
3. von Wasielewski R, Mengel M, Wiese B, Rüdiger T, Müller-Hermelink HK, Kreipe H. Tissue array technology for testing interlaboratory and interobserver reproducibility of immunohistochemical estrogen receptor analysis in a large multicenter trial. Am J Clin Pathol. 2002;118:675-82
4. Wasielewski von R, Hasselmann S, Rüschoff J, Fisseler-Eckhoff A, Kreipe H. Proficiency testing of immunohistochemical biomarker assays in breast cancer. Virchows Arch. 2008; 453:537-43.

Fine Needle Aspiration Cytology (4/20)

No further information

No references

Indications for Immediate Pathological Analysis Including Frozen Sections (5/20)

Further information and references:

Statement: Sentinel node biopsy for invasive cancer

Frozen section diagnosis of sentinel lymph nodes is used for detecting macrometastases (> 2mm), but inadequate to detect micrometastases or isolated tumor cells. Care must be taken not to lose too much tissue during frozen sectioning. Frozen sections should be restricted to cases with expected clinical consequences.

1. Kühn T, Bembenek A, Decker T et al. A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer 2005; 103: 451-461.
2. Grabau D, Rank F, Friis E. Intraoperative frozen section examination of axillary sentinel lymph nodes in breast cancer. APMIS 2005; 113: 7-12.
3. Van Diest PJ, Torrens H, Borgstein PJ et al. Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. Histopathology 1999; 35: 14-18.

Statement: Closest margin of resection

Margins of resection can be evaluated on frozen section if the macroscopic margin is less than 1 cm or if the macroscopic evaluation is doubtful. However, sensitivity and specificity is only 86% and 83% because of possible sampling errors in frozen sections. With macroscopically wider margins, the probability to detect tumor in the margin on frozen section is considered to be too low and therefore frozen section is not recommended with a macroscopic margin of > 1 cm.

For intraoperative radiotherapy free status of margins has to be assessed during operation. This is best done by macroscopical work-up of the unfixed specimen by a pathologist with only exceptional frozen sections.

1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthal R, Helfer L, Hrsg.). <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>
2. Kraus-Tiefenbacher U, Schara A, Steil V, Hermann B, Kehrer T, Bauer L, Melchert F, Wenz F. Intraoperative radiotherapy (IORT) for breast cancer using the Intrabeam system. Tumori. 2005;91:339-45

Statement: Lesions \geq 1 cm, without core biopsy

The diagnosis of malignancy can be established on frozen section for lesions that measure at least 1 cm in greatest dimension or larger. Smaller lesions should not be examined on frozen section because too much tissue may be lost.

1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthal R, Helfer L, Hrsg.). <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>
2. Fitzgibbons PL, Connolly JL, Page DL. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Arch Pathol Lab Med 2000; 124:1026- 1033. (ACR)
3. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006, pp 256-311

Statement: Non-palpable lesions or lesions $<$ 1 cm

Non-palpable lesions (e.g. biopsies performed because of microcalcifications) cannot not be evaluated adequately on frozen sections

1. Morrow M, Strom E, Bassett L et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin 2002; 52: 256-276.

General Recommendations for Specimen Handling (6/20)

Further information:

Statement: Adherence to sampling protocols and guidelines for accurate evaluation of tumor size and margins

To achieve consistent and clinically meaningful results standard procedures must be followed for sampling and reporting of breast pathology specimens. It is recommended to follow the national guidelines. This is especially important for the evaluation of surgical margins and reproducible determination of tumor size, extent of DCIS, and many other criteria that should be reported.

Statement: Consideration of clinical imaging results

The specimen workup must consider imaging results and indications for a given therapy (e.g. mastectomy). When relevant clinical information is unknown, workup of the specimen should be postponed.

Statement: Specimen radiography for non-palpable lesions and microcalcifications

As a rule, non-palpable lesions also cannot be seen by the naked eye of the pathologist. In order to sample the specimen adequately, e.g. to embed all microcalcifications, a specimen radiograph should be provided for or performed by the pathologist, ideally after slicing the specimen

Statement: Minimum fixation time 6-48 h to minimize shrinking artefacts and allow determination of angioinvasion

Many histological details are destroyed by too rapid processing of larger specimens. 24 h fixation time should be maintained before processing. Angioinvasion should be reported routinely (if unequivocal) and classified as blood vessel or lymphatic vessel invasion (if unequivocal). Distinguish peritumoral L1 from extensive L1 from L1 in skin. Report special situations (L1 in margins, skin, fascia, axillary fat). Not a prerequisite for diagnosis of inflammatory breast cancer.

Statement: Tissue banking to be performed by the pathologist

Tumor banking requires dissection of diagnostically relevant structures and therefore should be performed by the pathologist only.

References:

1. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006, pp 256-311
2. Fitzgibbons PL, Connolly JL, Page DL. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Arch Pathol Lab Med 2000; 124:1026- 1033. (ACR)
3. Morrow M, Strom EA, Bassett LW, et al. Standard for breast conservation therapy in the management of invasive breast carcinoma. CA Cancer J Clin 2002;52: 277-300 (ACR, ACoS, CAP, SSO)

Workup of Breast-Conserving Specimens (7/20)

Further information:

Statement: Slicing perpendicular to the longitudinal axis

As a rule, breast-conserving specimens are to be sliced into 0.3 – 0.5 sections perpendicular to the longitudinal axis of the specimen. In this way, it is assured that the minimal distance of the tumor to the margins can be assessed accurately.

Statement: Systematic sampling, at least 1 tissue block every 1 cm

To rule out tumor deposits in areas not suspicious to the naked eye, at least 1 tissue block every 1 cm should be sampled.

Statement: Inking of resection margins. Sampling of resection margins in all dimensions

The topographic relationship of the tumor within the specimen is best documented by imaging of the sliced specimen (either by radiography, photodocumentation or a diagram)

Statement: Documentation after slicing using specimen radiography, photodocumentation or diagram

The total size of a tumour is measured macroscopically and verified by microscopy. In case of discrepant results the microscopic measurement is taken as tumour size. In case of a DCIS component extending > 0.5 cm outside the margin of invasion, the total metric extent of the tumor and the DCIS component should be reported in addition to the size of the invasive carcinoma.

References:

1. Sinn HP, Anton HW, Magener A, von Fournier D, Bastert G, Otto HF.
Extensive and predominant in situ component in breast carcinoma: their influence on treatment results after breast-conserving therapy. Eur J Cancer. 1998 Apr;34(5):646-53.

2. Connolly JL, Boyages J, Nixon AJ, et al. Predictors of breast recurrence after conservative surgery and radiation therapy for invasive breast cancer. *Mod Pathol*. 1998;11:134-139.
3. Gage I, Schnitt SJ, Nixon AJ, et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer*. 1996;78:1921-1928

Workup of Mastectomy Specimens (8/20)

Further information:

Statement: Margins always to be sampled

- Skin close to tumor, at least 2 directions
- Deep margin
- Other margins, if close (< 1 cm)

Statement: Attention to soft tissue margins in skin sparing mastectomy

Statement: Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region

Statement: More extensive sampling in prophylactic mastectomies (BRCA-1 pos. patients)

These are minimal requirements for the workup of mastectomy specimens.

The statements are designed to make sure that clinically relevant information (e.g. multifocality, margins) is not missed.

References:

1. Fitzgibbons P, Connolly J, Page D. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Cancer Committee. Arch Pathol Lab Med 2000; 124: 1026-1033.
2. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8
3. A. Reiner-Concin, S. Lax. Mammakarzinom Pathologie. In: Manual der gynäkologischen Onkologie. Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) A. Reinthaller, L. Hefler (Hrsg.) <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>

Reporting of Invasive Carcinoma (9/20)

Further information:

Accurate pathological diagnoses and the provision of prognostically significant information are important to ensure that patients are managed appropriately and that the therapy is properly monitored and evaluated. A standard set of data from each patient, using the same terminology and diagnostic criteria is essential to achieve the latter objective. The opinions expressed here are based on the consensus view of the E.C. Working Group on Breast Screening Pathology [1] and take into account other consensus recommendations [2-8]. Special emphasis is put on the strict adherence and use of UICC and WHO classification systems and nomenclature [9, 10]. For grading of breast cancer, the Nottingham grading is recommended [11].

References:

1. Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006
2. Arbeitsgruppe Qualitätssicherung Pathologie in der konzertierten Aktion zur Brustkrebsfrüherkennung in Deutschland (2002). Anleitung Mammapathologie.
3. Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 2008.
http://www.senologie.org/download/pdf/s3_brustkrebsfrueherkennung_2008.pdf
4. Association of Directors of Anatomic and Surgical Pathology (1995). Recommendations for the reporting of breast carcinoma. Am J Clin Pathol 104:614–619
5. Connolly et al. Recommendations for the reporting of breast carcinoma. Association of Directors of Anatomic And Surgical Pathology. Mod Pathol (1996) vol. 9 (1) pp. 77-81
6. Henson DE, Oberman HA, Hutter RV (1997). Practice protocol for the examination of specimens removed from patients with cancer of the breast: a publication of the Cancer Committee, College of American Pathologists. Members of the Cancer Committee, College of American Pathologists, and the Task Force for Protocols on the Examination of Specimens from Patients with Breast Cancer. Arch Pathol Lab Med 121:27–33
7. Österreichische Gesellschaft für Pathologie (2000). Qualitätsstandards in der Pathologie
www.pathology.at/images/stories/PDF/Qualitaetsstandards/qsmamma.pdf
8. NHSBSP guidelines for pathology reporting in breast disease

9. UICC: TNM classification of malignant tumours, 6th ed (Sobin LH, Wittekind Ch, eds.). Wiley-Liss., Inc., New York New York (2002)
10. WHO. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. In: Tavassoli FA, Devilee P, eds. Lyon: IARC Press; 2003:9-112
11. Elston CW, Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 19 (1991) 403-410 (Canada)

Evaluation after Neoadjuvant Chemotherapy (10/20)

Further information:

Statement: Identification of tumor bed, otherwise ypTX

After neoadjuvant chemotherapy, the tumor bed must be identified in the specimen, and examined for completeness, size, and regressive changes. Without complete resection of the tumor bed, there is a chance of residual tumor, even in case of complete regression. Without positive identification of the tumor bed, the tumor status must be considered unknown, and therefore classified as pTX.

Statement: Reporting of tumor size as total extent of invasive carcinoma

Chemotherapy results in a variable loss of tumor cellularity with interspersed fibrotic areas, leading to an apparent multifocality. Tumor size after neoadjuvant chemotherapy should report the whole area where vital tumor cells can be detected. Only when tumor foci that are macroscopically distinct, this should be reported as multiple tumor foci, and the size of the largest focus taken for the ypT category.

Statement: Reporting of tumor regression according to Miller-Payne (2003), Symmans (2007) or Sinn (1994)

Various schemes for assessing tumor regression have been reported. Currently there is no preference for a single scheme, because no comparative data have been published. Among the most frequently used systems are Miller-Payne (2003), Symmans (2007), and Sinn (1994)

Statement: pCR is absence of invasive Ca. and absence of Lymphangiosis ca. or LN metastases (without consideration of DCIS)

There is consensus to use the term “pathologic complete remission” pCR for absence of invasive carcinoma. Lymph node metastases or residual DCIS may be present.

Statement: Use of IHC to identify tumor rests

Immunohistochemistry may be used to identify residual invasive tumor cells (e.g. in case of invasive lobular carcinoma with subtotal tumor regression), but is not required as a routine measure for the assessment of pCR.

References:

1. Pinder S.E., Provenzano E., Earl H., Ellis I.O. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. *Histopathology* 2007; 50(4):409-17
2. Ogston K, Miller I, Payne S et al. A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival. *Breast* 2003; 12: 320-327.
3. Symmans W, Peintinger F, Hatzis C et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25: 4414-4422.
4. Sinn H, Schmid H, Junkermann H et al. Histologische Regression des Mammakarzinoms nach primärer (neoadjuvanter) Chemotherapie. *Geburtshilfe Frauenheilkd* 1994; 54: 552-558.

Histologic Evaluation of Tumor Regression (11/20)

No further information

No references

Definition of pCR (12/20)

No further information

No references

ER, PgR Testing (13 + 14/20)

Further information and references:

Statement: Immunohistochemical detection on paraffin embedded (FFPE) tissue

1. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784-95.

Statement: Reporting percentage and intensity of pos. tumor nuclei (pos. if $\geq 1\%$)

The percentage of cells with nuclear staining using either estimation or quantitation. Quantitation may be done either by image analysis or manually. Entire slide should be reviewed to assess the tumor-containing areas. With limited tumor cells and little tumor staining must have at least 100 cells counted. Report an average intensity of tumor cell nuclei recorded as strong, moderate, or weak. Quantitative image analysis is encouraged for samples with low percentages of nuclear staining or in cases with multiple observers in the same institution. It is also a valuable way to quantify intensity and assure day-to-day consistency of control tissue reactivity.

1. Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

Statement: Allred Score (0 - 8)

Statement: Remmele Score (0 - 12)

A score may be provided if the scoring system is specified.

1. Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

Statement: Re-evaluation on excision specimen if triple-negative on core biopsy

If an external or internal control does not produce the expected reaction, the result of patient testing must not be reported. Instead, the assay should be repeated with the standard reagents under the standard conditions until acceptable ER and/or PgR reactivity of control material is achieved. No patient material should be reported until controls react appropriately.

If the particular histologic type of breast cancer is unlikely to be ER negative (tubular, mucinous, or lobular morphology or Nottingham score of 1), the tumor should also be subjected to confirmatory testing, such as sending the same specimen to a reference laboratory for retesting or by repeating the assay on another block or on a separate breast cancer specimen.

1. Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

Statement: Use of internal and external quality control schemes

Standardization of IHC reagents has been implemented by regulation of the FDA. Internally, most laboratories use control sections to validate their staining results. Supplementing these measures, standards should be compared between laboratories in interlaboratory trials. Such trials have focused on the quality of immunohistochemical stains or on standardized protocols for staining and specimen handling [1]. Quality control measures are mandatory in specialized breast units [2].

1. Rüdiger T, Hofler H, Kreipe HH et al. (2002) Quality assurance in immunohistochemistry: results of an interlaboratory trial involving 172 pathologists. Am J Surg Pathol 26:873-882
2. Deutsche Krebsgesellschaft und beteiligte medizinisch-wissenschaftliche Fachgesellschaften (2008). Interdisziplinäre Leitlinie Diagnose und Therapie des Mammakarzinoms der Frau. http://www.senologie.org/download/pdf/s3_ll_mammaca_11_02_2008.pdf

Other References:

1. Allred DC. Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Mod Pathol (2010) vol. 23 Suppl 2 pp. S52-9
2. Cheang MC, Treaba DO, Speers CH, Olivotto IA, Bajdik CD, Chia SK, Goldstein LC, Gelmon KA, Huntsman D, Gilks CB, Nielsen TO, Gown AM. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. J Clin Oncol. 2006 Dec 20;24(36):5637-44. Epub 2006 Nov 20.
3. Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

4. Rocha R, Nunes C, Rocha G, Oliveira F, Sanches F, Gobbi H. Rabbit monoclonal antibodies show higher sensitivity than mouse monoclonals for estrogen and progesterone receptor evaluation in breast cancer by immunohistochemistry. *Pathol Res Pract*. 2008;204(9):655-62. Epub 2008 Jun 18.

HER2-Testing (15 + 16/20)

Further information:

It was shown that the immunohistochemical HER2-determination (if necessary with subsequent FISH) is safe if performed on core biopsy [1]. In the comparison of the results between the core biopsy and excision specimens the hormone receptor results were more reliable tumor, suggesting the fixation of the excision specimen may be detrimental [4].

1. Chivukula M, Bhargava R, Brufsky A et al. (2008) Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. Mod Pathol 21:363-368

(abstracted from Ref. 4)

- The HER2 assay should only be evaluated in invasive breast cancer or the invasive component of the breast cancer.
- Required fixation of breast tissue samples is 10% neutral buffered formalin. Optimal fixation times are 6 to 48 hours and should be documented in the pathology report.
- HER2 determination in core biopsies is possible provided that enough tumour tissue is represented. The reliability of results on core biopsies has been shown to be between 82-100% [4-6]. Core biopsies offer the advantage of optimal and standardized fixation and neoadjuvant therapy requires analysis to be done on core biopsies. Centres have to validate their methods by systematic comparison of HER2 assessment in core biopsies and resection specimens, then the congruence will be >95% [7].
- Assay procedures must be validated by the laboratory before offering the test clinically. The test should show 95% concordance with a validated reference assay.
- Assay procedures must be standardized. Any deviation from the standardized method must be recorded and justified by revalidation of the method. Personnel performing assays must have their competency assessed at regular intervals.
- Standardized control materials, either purchased products or products conforming to defined manufacturing standards (for example, cell lines of the European Collection of Cell Cultures or those produced by the National Institute of Standards and Technology [NIST]) or defined by the laboratory director, must be consistently used by each laboratory with each run of tests. Adequate control materials include cell lines or tumor blocks with well defined negative, equivocal, and positive expression and gene amplification assay results. Faux tissue blocks or xenografts with variable HER2 expression levels may also be used if the results expected are well characterized. If controls do not show usual results, the assay must be repeated rather than interpreted.

- Image analysis can be an effective tool for achieving consistent interpretation. However, a pathologist must confirm the image analysis result.
- Standardized interpretation criteria for all types of HER2 tests must be used, based on the interpretation criteria from recent clinical trials and international experience.
- Laboratory proficiency testing is required, e.g. by participating in interlaboratory trials ("Ringversuche") of the Deutsche Gesellschaft für Pathologie, or UK NEQAS-ICC (UK National External Quality Assessment Scheme for Immunocytochemistry) or NordiQC.

References:

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-1672.
2. Romond EP, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-1684.
3. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25:118-45.
4. Jacobs T, Siziopikou K, Prioleau J et al. (1998) Do prognostic marker studies on core needle biopsy specimens of breast carcinoma accurately reflect the marker status of the tumor? Mod Pathol 11:259-264
5. Taucher S, Rudas M, Mader RM et al. (2004) Prognostic markers in breast cancer: the reliability of HER2/neu status in core needle biopsy of 325 patients with primary breast cancer. Wien Klin Wochenschr 116:26-31
6. Wood B, Junckerstorff R, Sterrett G et al. (2007) A comparison of immunohistochemical staining for oestrogen receptor, progesterone receptor and HER-2 in breast core biopsies and subsequent excisions. Pathology 39:391-395
7. Lebeau A, Turzynski A, Braun S, Behrhof W, Fleige B, Schmitt WD, Grob TJ, Burkhardt L, Hölzel D, Jackisch C, Thomssen C, Müller V, Untch M. Reliability of human epidermal growth factor receptor 2 immunohistochemistry in breast core needle biopsies. J Clin Oncol. 2010;28:3264-70
8. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013

Ki-67-testing

Ki-67 is helpful in determining the grade of tumors. G1 tumors usually show a Ki-67 index below 15% and G3 tumors exhibit a labeling index \geq 25%. In core biopsies Ki-67 is better suited to predict the final histological grade than mitotic counts. Whether a threshold of 14% is able to discriminate between the luminal A and B type awaits further research. Ki-67 determination has shown to be variable.

1. von Wasielewski R, Klöpper K, Lück HJ, Kreipe H. [Improvement of breast cancer grading in punch biopsies: grading with the Ki-67 marker]. Pathologe. 2006 Sep;27(5):337-45.
2. Mengel M, von Wasielewski R, Wiese B, Rüdiger T, Müller-Hermelink HK, Kreipe H. Inter-laboratory and inter-observer reproducibility of immunohistochemical assessment of the Ki-67 labelling index in a large multi-centre trial. J. Pathol. 2002;198:292-9
3. Kwok TC, Rakha EA, Lee AH, Grainge M, Green AR, Ellis IO, Powe DG. Histological grading of breast cancer on needle core biopsy: the role of immunohistochemical assessment of proliferation. Histopathology. 2010;57:212-9.

Intrinsic Breast Cancer Types (17/20)

No further information

No references

Triple-negative breast cancer (18/20)

No further information

No references

Evaluation of Sentinel Node Biopsy (19/20)

Further information:

Statement: Evaluation of sentinel node biopsy:

The aim of histological workup of sentinel nodes is to detect macrometastases (> 2 mm), and the histological techniques must be adequate to meet this aim. Therefore, it is recommended to work up sentinel lymph nodes using step sections of ≥ 500 μm in order to make certain not to miss a macrometastasis (Kühn 2005).

Statement: Full workup using step sections of ≥ 500 μm on paraffin embedded tissue

The additional use of immunohistochemistry (IHC) results in an increase of sensitivity to detect micrometastases and ITC. Because of the expense of routine IHC and the questionable benefit of detecting additional micrometastases, IHC is not recommended as a routine procedure.

The sensitivity of frozen sections on sentinel node biopsies to a large extent depends upon how extensive the workup of the paraffin section is, and therefore varies to a wide extent in the literature. If not performed adequately, frozen sections of sentinel nodes may lead to loss of tissue and diagnostic information.

Statement: Imprint cytology instead or in addition of frozen section

Imprint cytology has a similar sensitivity and specificity when compared with frozen section. However it requires special expertise and may be slower than frozen tissue section (Layfield, 2010, Limberis 2009).

Statement: RT-PCR for epithelial genes

RT-PCR for epithelial genes has been reported to have a similar sensitivity as frozen sections. Because of several disadvantages, the routine use of RT-PCR is discouraged. These disadvantages include:

- Not all breast cancers are positive for Ck19 and/or mammaplobin. Some of the most aggressive tumors, such as triple-negative breast cancers, are negative for Ck19 and mammaplobin.

- The use of RT-PCR precludes the classification of lymph node metastases according to TNM (micro-/macrometastases, ITC).
- In an unknown proportion of cases, axillary lymph nodes may contain benign epithelial inclusions.

References:

1. Cserni G. (2004) Surgical pathological staging of breast cancer by sentinel lymph node biopsy with special emphasis on the histological work-up of axillary sentinel lymph nodes. *Breast Cancer*. 11: 242-9
2. Grabau DA, Rank F, Friis E (2005). Intraoperative frozen section examination of axillary sentinel lymph nodes in breast cancer. *APMIS*. 113:7-12
3. Kühn T, Bembenek A, Decker T et al. (2005) A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. *Cancer* 103:451-461
4. Layfield et al. Intraoperative assessment of sentinel lymph nodes in breast cancer. *The British journal of surgery* (2011) vol. 98 (1) pp. 4-17
5. Limberis V, Romanidis C, Galazios G, Koutsougeras G, Papadopoulos N, Lambropoulou M, et al. Intraoperative estimation of sentinel lymph nodes in breast cancer by imprint cytology. *European journal of gynaecological oncology*. 2009;30(1):85-7.
6. Viale G, Zurrida S, Maiorano E, Mazzarol G, Prunerì G, Paganelli G, Maisonneuve P, Veronesi U. Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. *Cancer*. 2005 Feb 1;103(3):492-500.
7. Weaver DL, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, Harlow SP, Julian TB, Mamounas EP, Wolmark N. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med*. 2011;364:412-21.

Mutation or Expression Analysis (20/20)

No further information

No references



Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Prognostic and Predictive Factors

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Prognostic and Predictive Factors

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Definition

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A Prognostic Factor* is any parameter available at the time of interest e.g. primary diagnosis that correlates with disease-free or overall survival, in the absence of any therapy and, as a result, is able to correlate with the natural history of the disease.

A Predictive Factor is any parameter associated with response to a given therapy.

***as mentioned in this context represent markers of BC recurrence**

Further
Information

References

“Low absolute risk implies low absolute benefit”

Threshold?

Karp et al SABCS 2012: cumulative leucemia/MDS after 10 yrs 0.5 %

Martin et al SABCS 2010: chronic heart failure (at ten years) in 3.5 % after TAC

Quality Criteria

- **Biological hypothesis**
- **Simple and reliable determination method, quality assurance (QA) of the test**
- **Prospectively planned statistical evaluation (primary goal)**
- **Validation of clinical significance according to**
 - „Oxford Level of Evidence (LoE_{Ox2001})“ criteria and „Grades of Recommendation (GR)“
 - „Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE₂₀₀₉) and category of tumor marker study (CTS)
- **Clinical relevance for treatment decisions**

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Further
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References

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¹Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009

²Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011

³McShane, Hayes, J Clin Oncol 30: 4223 – 4232, 2012

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

| Category Element | A Prospective | B Prospective using archived samples | C Prospective/ observational | D Retrospective/ observational |
|---|---|--|--|---|
| Clinical trial | Prospective controlled trial (PCT) designed to address tumor marker | Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires Prospective randomized controlled trial (PRCT) | Prospective observational registry, treatment and follow-up not dictated | No prospective aspect to study |
| Patients and patient data | Prospectively enrolled, treated, and followed in PCT | Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest | Prospectively enrolled in registry, but treatment and follow-up standard of care | No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review |
| Specimen collection, processing, and archival | Specimens collected, processed, and assayed for specific marker in real time | Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion | Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion | Specimens collected, processed and archived with no prospective SOPs |
| Statistical design and analysis | Study powered to address tumor marker question | Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays | Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays | Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays |
| Validation | Result unlikely to be play of chance Although preferred, validation not required | Result more likely to be play of chance than A but less likely than C Requires one or more validation studies | Result very likely to be play of chance Requires subsequent validation studies | Result very likely to be play of chance Requires subsequent validation |

Revised Determination of Levels of Evidence using Elements of Tumor Marker Studies

| Level of Evidence | Category | Validation studies available |
|-------------------|----------|---|
| I | A | None required |
| I | B | One or more with consistent results |
| II | B | None or inconsistent results |
| II | C | 2 or more with consistent results |
| III | C | None or 1 with consistent results or inconsistent results |
| IV–V | D | Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility |

Requirements for a Marker-Based Test to Reach Level IB Evidence

- **1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.**
- **2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.**
- **3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.**
- **4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.**

Prognostic Factors I in Early Breast Cancer

| Factor | LoE _{Ox2001} | GR | AGO |
|--|-----------------------|----|-----|
| ➤ Tumor size | 1a | A | ++ |
| ➤ Nodal status | 1a | A | ++ |
| ➤ Distant metastases | 1a | B | ++ |
| ➤ Histological tumor type (colloid, mucinous, tubular etc.) | 2b | B | ++ |
| ➤ Grade (Elston&Ellis) | 2a | B | ++ |
| ➤ Age | 2a | B | ++ |
| ➤ Peritumoral lymphatic vessel and vascular invasion (L1 V1) | 2b | B | + |
| ➤ pCR after NACT* in (HR+/G3, HER2+, TN) | 1a | A | ++ |
| ➤ BMI | 1b | B | + |

* NACT = Neoadjuvant Chemotherapy

Reproducibility

- **ER/PR discordance central vs local $\approx 20\%$ (ASCO/CAP JCO 2010)**
- **HER2 inaccurate testing suspected in approximately 20% (ASCO /CAP JCO 2007)**
- **Impact of routine pathologic review in N0 BC: 20% changes : grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22%, pN1mi: 11% upstaged, 15% downstaged in central pathology review (Ann Oncol 2012)**
- **Consistency: 107 cases examined by 23 pathologists in 4 rounds: Grading: Kappa 0,53; LVI Kappa 0,38 (ECWGBSP, 1999) (Virchows Arch 1999)**

Critical Issues Regarding LoEs for Biomarkers

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It needs to be emphasized that the levels of evidence obtained by Oxford-criteria and CTS-criteria cannot be directly compared.

The prospectively-planned retrospective validation of a biomarker (CTS level 1) may be biased by an insufficient number of clinical trial samples used for the biomarker analysis.

This sample collection may not represent the reported outcome of the clinical trial. An optimal percentage of sample needed from clinical trials needed for optimal biomarker validation has not yet been established *

Prognostic Factors II in Early Breast Cancer

| Factor | LoE _{Ox2001} | GR | AGO |
|---|-----------------------|----|-----|
| ➤ ER / PgR | 2a | B | + |
| ➤ HER2 (IHC, FISH) | 2b | B | + |
| ➤ ER / PgR / HER2 as surrogate markers for molecular subtypes | 2b | B | + |
| ➤ uPA / PAI (Femtelle [®] ELISA) [§] in N0 | 1a | A | + |
| ➤ Proliferation markers | | | |
| ➤ Ki-67 before, during or after treatment | 2b | B | + |
| ➤ Mitotic activity Index (MAI) | 1a | A | + |

[§] Validated clinical data only available for this assay

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Commercially Available Molecular Tests

| | 70 gene signature (MammaPrint®) \$ | 21 gene Recurrence score (Oncotype DX®) \$ | 8 gene signature (Endopredict®) \$ | PAM 50 (Prosigna®) \$ |
|--|--|---|---|---|
| Provider | Agendia | Genomic Health | Sividon | NanoString |
| Type of assay | 70-gene assay | 21-gene recurrence score | 11-gene assay | 50-gene assay |
| Type of tissue | fresh frozen (technical validation for FFPE available) | FFPE | FFPE | FFPE |
| Technique | Microarrays for RNA | qRT-PCR | q-RT-PCR | qRT-PCR |
| Central lab | Yes | yes | no | no |
| Indication and population studied | prognostic N ₀₋₁ , <61 Jahre | prognostic N ₀₋₁ ER+ endocrine treated | prognostic (pre-) postmenopausal N ₀₋₁ ER+ HER2- endocrine treated | prognostic postmenopausal N ₀₋₁ ER+ HER2- endocrine treated |
| Clinical Validation | yes | yes | yes | yes |
| Registration | FDA clearance as "In Vitro Diagnostic Multivariate Index Assay (IVDMIA)" | Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab | CE-Mark | FDA 510(k) Clearance |

\$ Validated clinical data only available for this assay

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| | 70 gene signature (MammaPrint®) \$ | 21 gene Recurrence score (Oncotype DX®) \$ | 8 gene signature (Endopredict®) \$ | PAM 50 (Prosigna®) \$ |
|--|---------------------------------------|--|---------------------------------------|--|
| Prognosis after 5 yrs (late recurrences) | not separately shown | No | yes | yes |
| Predictive impact (chemotherapy benefit) | poorly validated | yes * | not shown | not shown |
| Prospective- retrospective evidence (% of recruited patients) | Multicenter validation | NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%) | ABCSG 6 (19%) ABCSG 8 (36%) | MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%) |
| Prospective evidence (pending) | MINDACT (completed) | TAILOR _x (n0, completed) RxPONDER (n1, ongoing) | - | - |

\$ Validated clinical data only available for this assay

* Trial performed before HER2 testing, HER2 positive patients may have been included

Prognostic Factors III in Early Breast Cancer

| Faktor | LoE ₂₀₀₉ | CTS | AGO |
|--|---------------------|-----|-----|
| ➤ Disseminated tumor cells (DTC, in bone marrow) | I | B | +/- |
| ➤ Circulating tumor cells (CTC, in blood, Cell Search®) \$ | I | B | +/- |
| ➤ Therapy decisions based on CTC phenotypes | III | C | - |
| ➤ 21 gene recurrence score (Oncotype DX®) \$ (N0-1 ER+ HER2-, endocrine treated) | | | |
| ➤ N0 | I | B | ++ |
| ➤ N1 | II | B | +/- |
| ➤ 8 gene signature (EndoPredict®) \$ (postmenopausal, N0-1 ER+ HER2-, endocrine treated) | | | |
| ➤ N0 | I | B | ++ |
| ➤ N1 | II | B | +/- |
| ➤ 70 gene signature (MammaPrint®), N0-1 | II | C | +/- |
| ➤ PAM 50 (Prosigna®) \$ (postmenopausal, N0-1 ER+ HER2-, endocrine treated) | II | B | +/- |
| ➤ IHC4 (central pathology, published algorithm) # | I | B | +/- |

* Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making

\$ Validated clinical data only available for this assay

Cuzick et al., J Clin Oncol 29: 4273-4278, 2011

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Neoadjuvant Systemic Chemotherapy Response Prediction I

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| Factor | CTS | LoE _{Ox2001} | GR | AGO |
|--|-----|-----------------------|----|-----|
| ➤ Young age | B | 1a | A | + |
| ➤ cT1 / cT2 tumors o. N0 o. G3 | B | 1a | A | ++ |
| ➤ Negative ER and PgR status | B | 1a | A | ++ |
| ➤ Triple negative breast cancer (TNBC) | B | 1a | A | ++ |
| ➤ Positive HER2 status | B | 1a | A | ++ |
| ➤ Non-lobular tumor type | B | 1a | A | + |
| ➤ Early clinical response | B | 1b | A | + |

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| Factor | LoE ₂₀₀₉ | CTS | GR | AGO |
|--|---------------------|-----|----|-----|
| ➤ PAM50 (Prosigna ^{\$}) | III | C | B | +/- |
| ➤ 70-Gensignatur (Mammaprint ^{\$}) | III | C | B | +/- |
| ➤ Ki-67 | I | B | A | + |
| ➤ Tumour infiltrating lymphocytes | II | B | B | + |
| ➤ <i>PIK3CA</i> mutation | II | B | B | + |

^{\$} Validierte klinische Daten nur verfügbar für diesen Assay

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| Factor | LoE _{Ox2001} | GR | AGO |
|---|-----------------------|----|-----|
| ➤ Endocrine therapy | | | |
| ➤ ER/PgR status | 1a | A | ++ |
| ➤ IHC staining intensity (ER/PgR) | 1a | A | + |
| ➤ Tamoxifen | | | |
| ➤ CYP2D6 polymorphism | 2b | D | - |
| ➤ Ovarian ablation | | | |
| ➤ Menopausal status | 1c | A | ++ |
| ➤ Aromatase inhibitors vs. Tamoxifen | | | |
| ➤ Menopausal status | 1c | A | ++ |
| ➤ ER/PgR/HER2 as single markers | 1c | A | - |
| ➤ Lobular subtype | 2b | B | + |
| ➤ Ki-67 high (published cutoffs > 11% and >14 %) | 2b | B | +/- |
| ➤ BMI | 2b | B | +/- |

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Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

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| Factor | LoE _{Ox2001} (\$ LoE _{Ox2009}) | GR (\$ CTS) | AGO |
|--|--|----------------|-----|
| ➤ Anti-HER2-Therapy | | | |
| ➤ HER2 | 1a | A | ++ |
| ➤ Adjuvant Chemotherapy | | | |
| ➤ uPA/PAI1 (Femtelle®) ELISA \$ | 1a | A | + |
| ➤ 21 gene recurrence score (Oncotype DX®) \$ | I \$ | B \$ | +/- |

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\$ Validated clinical data only available for this assay

Prognostic factors – Metastatic breast cancer

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| Factor | LoE ₂₀₀₉ | CTS | AGO |
|--|---------------------|----------------|-----|
| ➤ Circulating tumor cells (CTC in blood, Cell Search[®]) | | | |
| ➤ Prognosis | I | B ^a | + |
| ➤ Therapy decision solely based on dynamics of CTC over time | I | A ^a | - |
| ➤ Therapy decisions based on CTC phenotypes | III | C | -* |

* Study participation recommended

Prognostic and Predictive Factors (2/20)

Further information:

Data bases screened: Pubmed 2008 - 2011, ASCO 2003 – 2009, SABCS 2003 – 2009 , ECCO (n.d.), EBCC 2007 (n.d.). Cochrane data base (n.d.)

Guidelines screened:

- Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009: Goldhirsch A et al. Ann Oncol. 2008;20:1319-39.
- Canadian Medical Association (CMA, 2006: <http://www.cmaj.ca/cgi/content/full/158/3/DC1>)
- NCCN 2008: <http://www.medscape.com/files/editorial/articles/548868/breast.pdf>
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Reasons given for the particular evidence level:

Statement 1 (LoE 6): ref. 2 & 3 (retrospective RCT's, <10% Power)

Definition (3/20)

No further information

No references

Low Absolute Risk Implies Low Absolute Benefit (4/20)

Further information:

Adjuvant chemotherapy reduces breast cancer mortality by one third. However, the benefit is closely related to the absolute risk of this individual patient.

Especially in ER positive tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leucemia / MDS. Because of this, proper risk assessment is mandatory.

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Quality Criteria (5/20)

Further information:

Ranking of evidence is of pivotal importance for clinical decision-making. The Oxford Levels of Evidence (LoE_{Ox2001}) and Grades of Recommendations (GR) were originally released in 2001 by the Centre of Evidence Based Medicine (www.cebm.net).

These original Oxford LoE and Grades of Recommendation were modified in 2011. The authors simplified the Levels in several ways. For example, levels 1a-c were merged to level 1. The novel classification was also modified to represent the natural flow of a clinical encounter (diagnosis,

prognosis, treatment, benefits, harms). These modified Oxford LoE also apply to prognostic factors. In this case, Level 1 can be reached with “systematic review of inception cohort studies”. Based on study quality and effect size, levels LoE can be graded up or down.

Finally, the authors of the modified Oxford LoE state, that “levels be interpreted with a healthy dose of common sense and good judgment” .(1)

To improve the quality of research on biomarkers a guideline named REMARK (Reporting Recommendations of Tumor Marker Prognostic Studies) was defined. REMARK describes the informations which should be given when publishing a biomarker study such as study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. (2) Depending on the quality of a biomarker study, the Tumor Marker Utility Grading System was introduced assigning different levels of evidence to a certain marker. (3) To obtain the highest level of evidence, a marker had to be tested prospectively in a prospectively randomized clinical study. Recently a refined system for biomarker study design and evaluation that incorporates a revised level of evidence scale for tumor marker studies, including those using archived specimens, was introduced. (4) Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly, so more efficient indirect "prospective–retrospective" designs using archived specimens might reach level I evidence if validated with consistent results. This recommendation was recently elaborated on and finally resumed by the NCCN Task Force Report for evaluation of the clinical utility of tumor markers in oncology. (5,6)

In this chapter on prognostic and predictive factors the original Oxford LoE and the revised classification of Levels of Evidence using elements of tumor marker studies as proposed by Simon, Paik and Hayes, 2009 are used as applicable.

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4. Simon RM, Paik S, Hayes DF (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J. Natl. Cancer Inst.* 101 (21): 1446–1452. Available: doi:10.1093/jnci/djp335.
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6. Febbo PG, Ladanyi M, Aldape KD, Marzo AM de, Hammond ME et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *J Natl Compr Canc Netw* 9 Suppl 5: S1-32; quiz S33.

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination (6/20)

No further information

References:

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Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies (7/20)

No further information

References:

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McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232

Requirements of a Marker-Based test to Reach Level IB Evidence (8/20)

No further information

References:

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Prognostic Factors I in Early Breast Cancer (9/20)

No further information

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Reproducibility (10/20)

Further information:

Conventional pathology and immunohistochemistry is for methodological reasons subject to high inter-observer variability/variable reproducibility. ASCO-CAP guidelines estimate discordance between central and local pathology in about one fifth of cases for ER and PgR and HER2 status. MIRROR trialists report upgrading of N0 status by central pathological review in an comparable amount. Thus the clinician should be aware of potential problems and pitfalls when decision for adjuvant treatment is taken together with the patient.

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Critical Issues regarding LoEs for Biomarkers (11/20)

No further information

No references

Prognostic Factors II in Early Breast Cancer (12/20)

No further information

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Commercially Available Molecular Tests (13/20) and (14/20)

Further information:

Modern genomic platforms generate highly reproducible information about tumor biology, which has to be integrated during the next years to clinical routine. Since the additive clinical information is highly correlated to the validation sets the commercially available tests have been enumerated separately together with their retrospective-prospective evidence and future evidence projected for > 2015 from prospective randomized trials. ASCO- guidelines already integrated uPA/PAI1 and Oncotype DX®. German AGO members still feel that prospective evidence should be generated before general recommendation. According to the consensus (see Ärzteblatt Stellungnahme der AGO Kommission Mamma) use in selected cases is recommended.

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Prognostic Factors III in Early Breast Cancer (15/20)

No further information

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IHC4

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Neoadjuvant Systemic Chemotherapy – Response Prediction I (16/20)

Further information:

This slide is based on the evidence mainly from analyses done by GEPAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides.

Ki 67 data from GEPARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤ 15 and > 35 are presumed to define low and high risk populations.

For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and MammaPrint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs.

The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

References:

TIL

Denkert, C., Loibl, S., Noske, A., Roller, M., Müller, B.M., Komor, M., Budczies, J., Darb-Esfahani, S., Kronenwett, R., Hanusch, C., Törne, C. von, Weichert, W., Engels, K., Solbach, C., Schrader, I. & Dietel, M. et al. 2010. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.

Neoadjuvant Systemic Chemotherapy – Response Prediction II (17/20)

Further information:

This slide is based on the evidence mainly from analyses done by GEPAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides.

Ki 67 data from GEPARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤ 15 and > 35 are presumed to define low and high risk populations.

For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and MammaPrint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs.

The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

References:

TIL

Denkert, C., Loibl, S., Noske, A., Roller, M., Müller, B.M., Komor, M., Budczies, J., Darb-Esfahani, S., Kronenwett, R., Hanusch, C., Törne, C. von, Weichert, W., Engels, K., Solbach, C., Schrader, I. & Dietel, M. et al. 2010. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J. Clin. Oncol. 28, 105–113. doi:10.1200/JCO.2009.23.7370.

Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides ample evidence that hormone receptor status is predictive for endocrine response, whereas little effect can be attributed to tumor size, nodal status, age and grading. According to the ASCO /CAP guidelines the panel recommended endocrine therapy in patients whose breast tumors show at least 1% ER positive cells. Same is true for PR receptor levels. HER2 overexpressing tumors present primarily with more aggressive biology. HER2 overexpression, quantitative ER and PR expression as single markers do not identify patients with better outcome after AI, when compared to TAM. (Dowsett M)

Cyp2D6 polymorphism detection is not recommended in daily routine as the metaanalysis done by Goertz is not conclusive.

ABCSG12 trialists, who compared AI + Goserelin vs Tam in premenopausal women report a nearly 50% increase in the risk of disease recurrence (HR 1.49) and a three-fold risk of death for overweight patients (BMI > 25) receiving AI+ Gos in comparison to TAM. In postmenopausal women ATAC trialist report a nonsignificantly better relative benefit of AI vs Tam in thin women vs overweight women (BMI > 35).

A retrospective analysis from a representative subgroup of more than 2500 patients from BIG 1-98 demonstrated a strong correlation of AI superiority with invasive lobular histology and luminal B like tumors (ER+/PR+/Ki 67 >14, HER2-). The HR were 0.95 for ductal luminal A, 0.64 for ductal luminal B, 0.49 for lobular luminal a and 0.33 for lobular luminal B.

No references

Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy (19/20)

Further information:

Her2 overexpression (IHC, FISH) is highly predictive for anti HER2 therapy. During SABCS 2012 Baselga presented biomarker analyses evaluating patients with higher benefit from addition of pertuzumab from the CLEOPATRA trial. Neither HER2 or HER3 (mRNA), nor EGFR (mRNA) were predictive.

The last EBCTCG metaanalysis involving over 100 000 chemotherapy patients from 123 randomized trials demonstrated proportional risk reduction little affected by age, nodal status, tumor diameter, HR status and grading. The evidence for HER2 overexpression is much less well evaluated. Most data are derived from trials evaluating chemotherapy + endocrine therapy versus endocrine therapy alone in HR+ patients (Viale IBCSG VIII + IX, Albain SWOG 8814 and Paik NSABP B-20). Uniformly the degree with chemotherapy interaction is non significant independently whether evaluated by central DAKO Hercept testing or her2 gene group as part of Oncotype DX.

The prospectively randomized chemo N0 trial demonstrated that high levels of upA/PAI-1 are associated to increased CMF chemotherapy benefit. In N0-1/HR+ patients the same has been demonstrated by retrospective analyses from the prospective trials NSABP – B20 and SWOG 8814 for CAF/Tam vs Tam alone. In N0 patients from B-20 the RR was 0.26, 0.61 and 1.31 for high risk, intermediate risk and low risk patients, with a net chemotherapy benefit of 28 % 10 year distant free survival benefit in the high risk group. In SWOG 8814 evaluating N+ patients the HRs for 5 yr overall survival were 0.56 in the high risk group, 0.84 in the intermediate and 1.18 in the low risk group resulting in a net 10 yrs dfs benefit of 12 % for the high risk group.

Data for Mammaprint (Knauer et al) refer to 541 patients from pooled study series from patients who received endocrine therapy +/- chemotherapy. In the high risk group the univariate HR was 0.21 ($p < 0.01$) compared to 0.58 ($p = 0.6$) in the low risk group. For other genomic signatures there are no data. PAM50 has been only evaluated in a neoadjuvant setting as surrogate parameter for pCR and Endopredict data refer to patients treated with endocrine therapy only.

Baseline Ki-67 is as Viale et al demonstrated from retrospective analyses of two IBCSG trials no independent predictor of chemotherapy outcome. Retrospective subgroup analyses of patients from large taxane trials (GEICAM, PACS 01, BCIRG 01, EC-Doc) demonstrate that luminal A like tumors identified by IHC are likely to have small benefit, but these third generation trials do not have endocrine only arms.

HER2 overexpression was highly predictive for anthracycline outcome, when compared to CMF. In a subgroup of the patients analysed by Gennari Di Leo published a metaanalysis comparing the impact of Her2 status and TOP2A (FISH). The HR for her2 amplification and non amplification were 0.89 and 0.71 respectively. Those for Topo normal versus Topo altered were 0.88 vs 0.64 respectively.

TOP2A coamplification, not HER2 amplification, is the clinically useful predictive marker of an incremental response to anthracycline-based chemotherapy.

Response to taxanes has been evaluated in different third generation trials comparing anthracycline based chemotherapy vs taxane/anthracycline based regimens. Identification of low proliferating tumors by central ki-67 evaluation was predictive for taxane outcome in EC-Doc, BCIRG 001 and PACS 001, but not in the GEICAM trial. Endopredict and Oncotype DX did not predict taxane response in the GEICAM trial and in NSABP B28 respectively.

No references

Prognostic factors – Metastatic breast cancer (20/20)

No further information

References:

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Lesions of Uncertain Malignant Potential (B3)

START

(ADH, LIN, FEA, Papilloma, Radial Scar)

Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

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Pathology Reporting for Minimal Invasive Biopsies

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B – Classification*

B1 = unsatisfactory / normal tissue only

B2 = benign lesion

B3 = lesion of uncertain malignant potential

B4 = suspicion of malignancy

B5 = malignant

B5a = non-invasive

B5b = invasive

B5c = in-situ/invasion not assessable

B5d = non epithelial, metastatic

* National Coordinating Group for Breast Screening Pathology (NHSBSP), E.C.
Working Group on Breast Screening Pathology, S3-Leitlinien

B3-Lesions

- **Lesions with risk of associated DCIS or invasive Ca:**
 - **Atypical ductal hyperplasia (ADH)**
 - **Lobular neoplasia (ALH, LCIS)**
 - **Flat epithelial atypia (FEA)**
- **Inhomogenous lesions with sampling risk:**
 - **Phyllodes tumor, cellular fibroadenoma**
 - **Papilloma, if incompletely removed**
 - **Radial scar, complex sclerosing lesion**

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Management after Minimally Invasive Biopsy

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➤ **Interdisciplinary conference: Concordant findings in pathology and imaging?**

→ yes: proceed according to histologic type

3a C ++

→ no: open biopsy

3a C ++

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Atypical Ductal Hyperplasia (ADH)

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- Synonyms: Atypical intraductal epithelial proliferation (AIDEP)
- Definition: Atypical intraductal proliferations with cytologic and structural features of well differentiated DCIS, such as rigid bridging or micropapillae, well demarcated cell borders and occupy less than two separate duct spaces. The extension of all involved lumina within one ductulo-lobular unit is less than 2 mm. Atypical ductal proliferations larger than 2 mm or in at least two ductules are classified as DCIS (low-grade).
- Indicator/Precursor lesion: Ipsi- and contralateral breast cancer risk: RR 3 - 5 x after 3 - 5 years.
- Classification in ductal intraepithelial neoplasia grade 1 - 3 is not sufficiently validated.

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Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)

Stratification of breast cancer risk*

| | | |
|------------------------|-------------|-----------|
| ➤ Number of Foci: | 1 | RR = 2,33 |
| | 2 | RR = 5,26 |
| | ≥ 3 | RR = 7,97 |
| ➤ Microcalcifications: | present | RR = 3,21 |
| | not present | RR = 4,21 |
| ➤ Type | ductal | RR = 3,83 |
| | lobular | RR = 3,67 |
| | both | RR = 7,10 |
| ➤ Age | < 45 | RR = 6,76 |
| | 45 – 55 | RR = 5,10 |
| | > 55 | RR = 2,67 |

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*AC Degnim et al. J Clin Oncol 2007; 25: 2671-2677

Strategy after Diagnosis of ADH

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ADH in core- / vacuum-assisted biopsy:

- Open excisional biopsy 3a C ++
- Open excisional biopsy may be omitted, with:
 - a) A small lesion (≤ 2 TDLU* in vacuum biopsy) and
 - b) Complete removal of imaging abnormality 5a C +

ADH at margins in resection specimen:

- No further surgery, if incidental finding accompanying invasive or intraductal carcinoma 3a C ++

* Terminal ductal-lobular unit

Lobular Intraepithelial Neoplasia (LIN)

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- Includes: Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN1 - 3 classification is not sufficiently validated prognostically
- Pleomorphic LIN and LIN with are classified as → **B5a**
- Indicator/Precursor lesion:
Ipsi- and contralateral enhanced breast cancer risk:
7 x at 10 years

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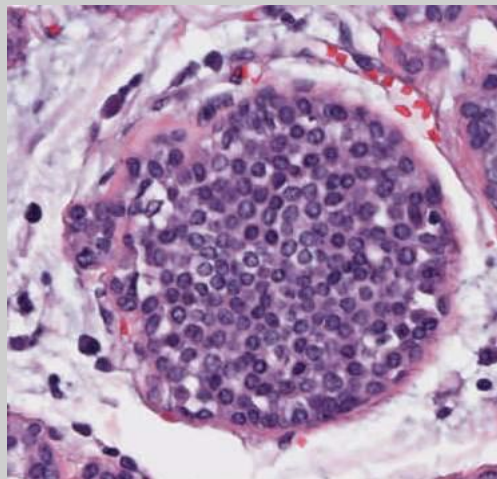
Further
Information

References

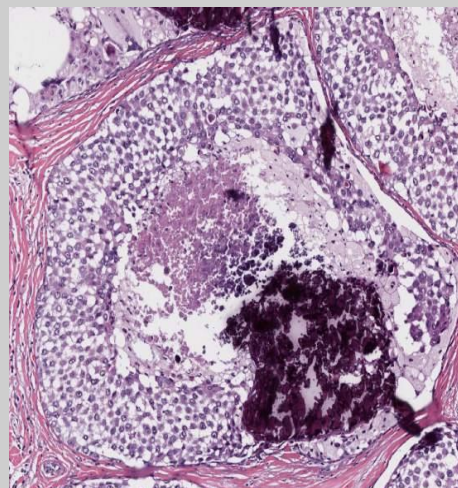
Variants of Lobular Neoplasia

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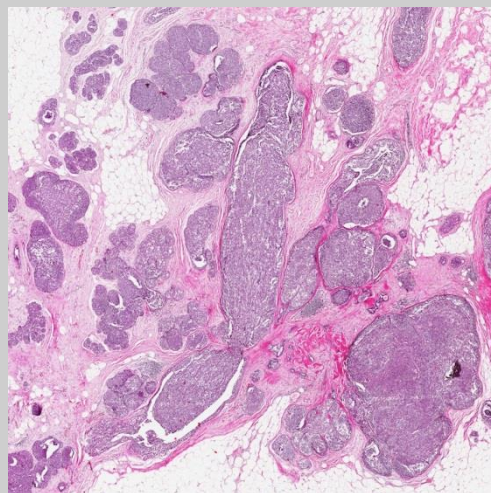
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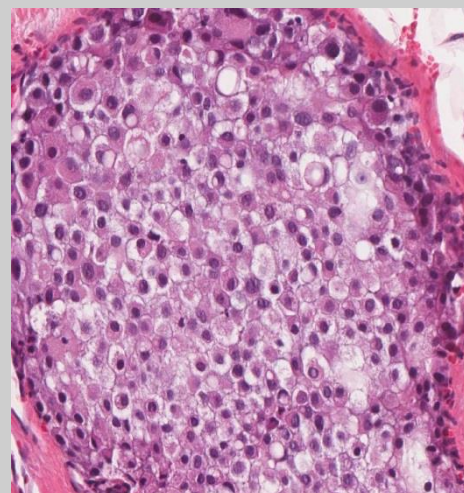
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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LIN with High Risk

- Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necroses, microcalcifications
- Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighbouring TDLU
- Type of LCIS with 21 cases of LCIS with microinvasion*:
 - classical LCIS: n=11
 - florid LCIS: n=4
 - pleomorphic LCIS: n=1

Strategy after Diagnosis of LIN

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| | | | |
|---|----|---|----|
| ➤ <u>LIN in core- / vacuum-assisted biopsy:</u> | | | |
| → Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings | 2b | C | ++ |
| ➤ <u>LIN at margins of resection specimen (BCT):</u> | | | |
| → No further surgery | 3a | C | ++ |
| <u>Exceptions:</u> | | | |
| a) Pleomorphic LIN, florid LIN, or LIN with necrosis | | | |
| b) Imaging abnormality is not removed | | | |
| → Complete resection | 5 | D | ++ |

Flat Epithelial Atypia (FEA)

- Synonyms: Columnar cell hyperplasia with atypia, columnar cell metaplasia with atypia, ductal intraepithelial neoplasia grade 1A (DIN 1A)
- Differential diagnosis:
 - ADH is discriminated by architectural features (micropapillary, cribriform) → **B3**
 - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as → **B5a**
- Marker lesion:

FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, correlation with imaging is mandatory.

Strategy after Diagnosis of FEA

**Oxford / AGO
LoE / GR**

➤ **FEA in core biopsy/vacuum-assisted biopsy:**

→ Open excisional biopsy

3b C +

→ Open excisional biopsy may be omitted, with:

**a small lesion (≤ 2 TDLU* in vacuum biopsy) and
complete removal of imaging abnormality**

5a C +

➤ **FEA at margins in resection specimen:**

3b C ++

→ No further surgery, unless calcifications have not been completely removed

* Terminal ductal-lobular unit

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Papilloma

- Includes: central papilloma, large duct papilloma, major duct papilloma, intraductal papilloma, atypical intraductal papilloma (B3)
- To be discriminated from papilloma with DCIS and from peripheral papillomas arising in the TDLU, size ≤ 2 mm, may be multiple
- To be discriminated from intraductal papillary carcinoma and encapsulated papillary carcinoma
- Indicator lesion:
May be associated with in-situ or invasive cancer (10%, in case of atypical papilloma up to 20%), increased ipsilateral risk for cancer (4.6% to 13% in case of atypical papilloma)

Strategy after Diagnosis of Central Papilloma

Oxford / AGO
LoE / GR

➤ **Papilloma in core- / vacuum-assisted biopsy:**

→ Open excisional biopsy

3a C ++

➤ **Papilloma at margins of resection specimen:**

→ No study data available

Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radial configuration.
- Includes:
 - radial scar
 - complex sclerosing lesion (> 1 cm)
- Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)
- Risk for upgrade in open biopsy after diagnosis of radial-sclerosing lesion in core biopsy: 8.3% (79/948)*

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* Bianchi S et al. Breast. (2012) 21: 159–64.

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

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➤ Radial scar / CSL in core biopsy/ vacuum-assisted biopsy:

→ Open excisional biopsy

→ Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality

**Oxford / AGO
LoE / GR**

3b C +

5a C +

➤ Radial scar / CSL at margins in resection specimen:

→ No further surgery, unless calcifications have not been completely removed

3b C ++

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Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

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FEA, non-atypical Papilloma

- Screening mammography

LIN

- Mammography (12 months)

ADH

- Mammography (12 months)

- Women with LIN and ADH should be informed about their elevated risk of breast cancer

**Oxford / AGO
LoE / GR**

5 C ++

3a C ++

3a C ++

3a C ++

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Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

Oxford / AGO LoE / GR

- | | | | | |
|--|----|---|----|-----|
| ➤ Tamoxifen for women >35 years – Risk reduction of invasive BrCa and DCIS | 1a | A | + | * |
| ➤ Raloxifen for postmenopausal women - Risk reduction of invasive BrCa only | 1b | A | + | * |
| ➤ Aromatase inhibitors for postmenopausal women | 5 | D | +/ | -** |

Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

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*Risk situation as defined in NSABP P1-trial (1,66% in 5 years)

** Study participation recommended

Outcome of Medical Prevention (1)

NSABP-P1 Study , update 2005

| | Placebo Rate / 1000 WE | Tamoxifen Rate / 1000 WE | RR | 95% CI |
|---|------------------------------|-----------------------------|-------------|------------------|
| All women | 6.29 | 3.59 | 0.57 | 0.46-0.70 |
| w/o LCIS | 5.93 | 3.41 | 0.58 | 0.46-0.72 |
| W LCIS | 11.70 | 6.27 | 0.54 | 0.27-1.02 |
| w/o AH | 5.87 | 3.69 | 0.63 | 0.50-0.78 |
| w AH | 10.42 | 2.55 | 0.25 | 0.10-0.52 |
| 5 y risk <2% | 4.77 | 3.18 | 0.67 | 0.43-1.01 |
| 5 y risk > 5% | 11.98 | 5.15 | 0.43 | 0.28-0.64 |
| One 1 st ° relatives | 6.47 | 3.48 | 0.54 | 0.34-0.83 |
| >= three 1st ° relatives | 11.24 | 5.48 | 0.49 | 0.16-1.34 |
| Fractures | 2.88 | 1.97 | 0.91 | 0.51-0.92 |
| Endometrial Ca | 0.68 | 2.24 | 3.28 | 1.87-6.03 |

Should only be offered to women at high risk, e.g.

- with LIN
- with ADH
- with a strong family history

NSABP-P2 Study, STAR trial 2006

| | Tamoxifen Rate / 1000 WE | Raloxifen Rate / 1000 WE | RR | 95% CI |
|--|--------------------------------|-----------------------------|-------------|------------------|
| All women | 4.30 | 4.41 | 1.02 | 0.82-1.28 |
| W/O LCIS | 3.76 | 3.89 | 1.03 | 0.81-1.33 |
| W LCIS | 9.83 | 9.61 | 0.98 | 0.58-1.63 |
| W/O AH | 4.06 | 4.03 | 0.99 | 0.76-1.28 |
| W AH | 5.21 | 5.81 | 1.12 | 0.72-1.74 |
| 5 y risk <3% | 2.03 | 2.83 | 1.40 | 0.87-2.28 |
| 5 y risk > 5% | 6.77 | 7.35 | 1.09 | 0.78-1.52 |
| One 1 st ° relatives | 4.99 | 5.18 | 1.04 | 0.69-1.55 |
| >=two 1st ° relatives | 5.16 | 5.00 | 0.97 | 0.60-1.56 |
| Endometrial CA | 2.00 | 1.25 | 0.62 | 0.35-1.08 |
| Thromboembolisms | 3.71 | 2.61 | 0.70 | 0.54-0.91 |
| Develeoping Cataracts | 12.30 | 9.72 | 0.79 | 0.68-0.92 |

Should not be offered to women

- with a moderate risk over the age of 50
- with an increased risk for thromboembolic events

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Outcome of Medical Prevention (2)

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**Risks and benefits with long-term Tamoxifen use compared with placebo: results from the IBIS-I Trial, 96 months median follow-up
(Cuzick J et al J Natl Cancer Inst 2007:272-282)**

| | RR | 95% CI | AR per 1000* | NNT / NNH** |
|---|-------------|------------------|--------------|-------------|
| BC Incidence | 0.73 | 0.58-0.91 | 15 | 68 |
| Invasive BC | 0.74 | 0.58-0.94 | 12 | 81 |
| Thromboembolism | 1.72 | 1.27-2.36 | 14 | 73 |
| Deep vein thrombosis | 1.84 | 1.21-2.82 | 9 | 115 |
| Headache | 0.93 | 0.87-0.99 | 25 | 39 |
| Gynecological / vasomotoric symptoms | 1.08 | 1.06-1.10 | 64 | 16 |
| Breast complains | 0.77 | 0.70-0.84 | 58 | 17 |

Risk communication:

AR*: absolute risk difference per 1000 women

NNT/NNH number needed to treat or number needed to harm only shown for statistically significant events over the entire follow-up period**

Data computed by guideline authors Visvanathan K et al. JCO 2009;27:3235-3258

Lesions of Uncertain Malignant Potential (B3) (2/22)

Further information:

Search:

Lobular neoplasia (135 Results): (Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh] OR Breast Diseases/US[mh]) AND ("2005/01/01"[dp] : "2014/01/01"[dp]) AND ("lobular neoplasia"[ti] OR "lobular intraepithelial neoplasia"[ti] OR "atypical lobular hyperplasia"[ti] OR "lobular carcinoma in situ"[ti] OR "LIN"[ti] OR "ALH"[ti] OR "LCIS"[ti]) AND ("english"[la] OR "german"[la])

Atypical ductal hyperplasia (65 Results): (Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh] OR Breast Diseases/US[mh]) AND ("2005/01/01"[dp] : "2014/01/01"[dp]) AND ("atypical ductal hyperplasia"[ti] OR "atypical hyperplasia"[ti] OR "ADH"[ti]) AND ("english"[la] OR "german"[la])

Flat epithelial atypia (79 Results): (Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh] OR Breast Diseases/US[mh]) AND ("2005/01/01"[dp] : "2014/01/01"[dp]) AND ("flat epithelial atypia"[ti] OR "columnar cell"[ti] OR "FEA"[ti]) AND ("english"[la] OR "german"[la])

Papilloma (227 Results): (Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh] OR Breast Diseases/US[mh]) AND

("2005/01/01"[dp] : "2014/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[Title]

Radial scar (17 Results): (Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh] OR Breast Diseases/US[mh]) AND ("2005/01/01"[dp] : "2014/01/01"[dp]) AND ("radial scar"[ti] OR "complex sclerosing lesion"[ti] OR "radial sclerosing lesion"[ti]) AND ("english"[la] OR "german"[la])

Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.I.2014
- NCCN Breast Cancer Risk Reduction I 2013
- NCCN Breast Cancer Screening and Diagnosis 2.2013
- NZ: HTA risk assesment 2007
- CMJA: no update
- NICE: no update
- SIGN: no update
- Cochrane: Decision aids for risk communication update 2009
- DARE: no relevant references. 2010
- ASCO 2012: done
- National Institute of health (NIH): done
- San Antonio Breast Cancer Conference (SABCC 2013): done

References

National and international guidelines

1. Albert US, Altland H, Duda V et al. 2008 update of the guideline early detection of breast cancer in Germany. J Cancer Res Clin Oncol 2009; 135:339-354
2. Albert US, (Hrsg). Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 1.Aktualisierung 2008. 1 ed. Muenchen: Zuckschwerdt Verlag, 2008.
3. Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL
4. Lebeau A, Kreipe H, Dietel M, Schlake W, Kreienberg R. Mammakarzinom: aktuelle Empfehlungen für Pathologen auf Basis der S3-Leitlinie. Pathologe. 2013;34(4):293-302
5. Visvanathan K, Chlebowski R, Hurley P et al. American Society of Clinical Oncology Clinical Practice Guideline: Update on the use of pharmacologic interventions including tamoxifen, raloxifen and aromatase inhibition for breast cancer risk reduction. JCO 2009; 27:3235-3258
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8. NCCN, National Comprehensive Cancer Network. Breast cancer risk reduction V.I.2013. 2013 ed. USA: NCCN, 2013.
9. NCCN, National Comprehensive Cancer Network. Breast cancer screening and diagnosis V.2.2013. 2013 ed. USA: NCCN, 2013.
10. O'Connor A, Bennett C, Stacey D et al. Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-35.

Pathology Reporting for Minimal Invasive Biopsies (3/22)

Further information:

The histologic B-classification of breast core biopsies as based on recommendations of the National Coordinating Group for Breast Screening Pathology (NHSBSP), and the European Commission Working Group on breast screening pathology

References:

1. World Health Organization: WHO Classification of Tumours of the Breast. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, editors. World Health Organization; 2012.
2. Wells C: Quality assurance guidelines for pathology: Cytological and histological non-operative procedures. In: European guidelines for quality assurance in breast cancer screening and diagnosis. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, Karsa von L, editors. Luxembourg: Office for Official Publications of the European Communities, 2006: 221-256
3. NHSBSP. Guidelines Working Group of the National Coordinating Committee for Breast Pathology. Pathology reporting of breast disease. Sheffield: NHS Screening Programmes and The Royal College of Pathologists, 2005.

B3 Lesions (4/22)

Further information:

Lesions of uncertain malignant potential include atypical ductal hyperplasia (ADH), lobular neoplasia (LN), flat epithelial atypia (FEA), atypical papillary proliferations, and lesions with sampling risk because of inhomogeneity, such as phyllodes tumor, cellular fibroadenoma, and radial scars. The lesions with atypical proliferations (ADH, ALH, LCIS, FEA) are regarded both as an indicator of increased risk, but also as precursor lesions, and are part of the low-grade pathway of breast cancers [1-4]. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient, and to decide if the lesion should be excised. The recognition of atypical epithelial proliferation is based on the distinction of hyperplastic from neoplastic lesions, that is on the identification of a clonal process. As a general rule, usual type epithelial hyperplasia is morphologically and phenotypically heterogeneous, while ADH, FEA, and LN are characterized by a homogeneity of cell type and marker expression. With all types of precursor lesions, careful attention must be paid to the pathologic-radiologic correlation for the guidance of the clinical management. B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1,3% discordance for B5 lesions [5].

References:

1. Andreu FJ, Sáez A, Sentís M, Rey M, Fernández S, Dinarès C, et al. Breast core biopsy reporting categories--An internal validation in a series of 3054 consecutive lesions. *Breast*. 2007 Jan 31;16(1):94–101.
2. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. Ladanyi M, Hogendoorn PC, editors. *J Pathol*. 2010 Nov 16;223(2):308–18.

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4. Houssami N, Ciatto S, Bilous M, Vezzosi V, Bianchi S. Borderline breast core needle histology: predictive values for malignancy in lesions of uncertain malignant potential (B3). *Br J Cancer*. 2007 Apr 22;96(8):1253–7.
5. Kreipe H-H, Höfler H, Lebeau A, Pickartz H, Schmidt D. Ergebnisse der Referenzpathologie im Mammographie-Screening. *Pathologe*. 2008 Oct 9;29(S2):178–80.

Management after Minimal Invasive Biopsy (5/22)

Further information:

What kind of treatment has to follow when a B3 diagnosis has been rendered should be individually determined in an interdisciplinary discussion of the imaging findings and the pathology results. Algorithm for quality assurance of minimal invasive guided biopsies.

After a review and quality assessment of 21 studies, diagnostic accuracy of VAB were evaluated. The summary estimates for VAB in diagnosis of breast carcinoma were as follows: sensitivity, 0.981 (95% confidence interval [CI], 0.972-0.987); specificity, 0.999 (95% CI, 0.997-0.999); positive likelihood ratio (PLR), 93.84 (95% CI, 41.55-211.95); negative likelihood ratio, 0.05 (95% CI, 0.03-0.09); diagnostic odds ratio, 1891.7 (95% CI, 683.8-5233.4); underestimate rate of ADH and DCIS were 20.9% (95% CI, 0.177-0.245) and 11.2% (95% CI, 0.098-0.128), respectively. VAB is a highly sensitive and specific biopsy method for evaluating mammographically detected breast in women.

References:

1. Brem RF, Behrndt VS, Sanow L, Gatewood OM: Atypical ductal hyperplasia: histologic underestimation of carcinoma in tissue harvested from impalpable breast lesions using 11-gauge stereotactically guided directional vacuum-assisted biopsy. AJR 1999, 172:1405-1407
2. Ciatto S, Houssami N, Ambrogetti D, Bianchi S, Bonari R, Brancato B, Catarzi S, Risso G: Accuracy and underestimation of malignancy of breast core needle biopsy: the florence experience of over 4000 consecutive biopsies. Breast Cancer res Treat 2007, 101:291-307
3. Bedei L, Falcini F, Sanna P: Atypical ductal hyperplasia of the breast: the controversional management of a

borderline lesion. Experience of 47 cases diagnosed at vacuum-assisted biopsy. *Breast* 2006, 15:196-202.

4. Liberman L, Holland A, Marjan D, Murray M, Bertelle L, Morris E, Dershew D, Wynn R: Underestimation of atypical ductal hyperplasia at MRI-guided 9-Gauge vacuum-assisted breast biopsy. *AJR* 2007, 188:684-690.
5. Zagrafos G, Zagouri F, Sergeantanis T, Nonni A, Koulocheri D, Folou M, Panopoulou E, Paranas N, Foliadis C, Bramis J: Minimizing underestimation rate of microcalcifications excised via vacuum-assisted breast biopsy: a blind study. *Breast Cancer Res and Treat* 2008, 109:397-402.
6. Arora S, Menes T, Moungh C, Nagi C, Bleiweiss I, Jaffer S. Atypical ductal hyperplasia at margin of breast biopsy - Is Re-excision indicated? *Ann Surg Oncol* 2007; 15(3):843-847

Atypical Ductal Hyperplasia (ADH) (6/22)

Further information:

The term atypical ductal hyperplasia (ADH) has been defined to describe small atypical ductal lesions with insufficient criteria for a definite diagnosis of DCIS. However, there is no general agreement on diagnostic criteria to distinguish ADH from low grade DCIS, and different definitions have been applied. Uncommon variants of ADH include atypical apocrine hyperplasia and atypical ductal proliferations developing within a pre-existing benign proliferative lesion such as sclerosing adenosis. Clonality is recognised by uniformity of morphology and phenotype, but also markers such as cytokeratin expression or hormone receptor expression can be used. Clinically, an excisional biopsy is recommended when ADH is identified in core-needle biopsy or in a vacuum-assisted biopsy specimen, but has no further consequences when found in a resection specimen, associated with benign lesions. The upgrade risk for ADH in a minimally invasive biopsy is estimated at 28% after open excision [1].

ADH and breast cancer are associated with postmenopausal hormone treatment. According to the data of the Breast Cancer Surveillance Consortium (USA) rates of ADH decreased from 5.5/10000 mammograms 1999 to 2.4/10000 mammograms in 2005.

References:

1. Menes T: Rates of atypical ductal hyperplasia have declined with less use of postmenopausal hormone treatment: Findings from the Breast Cancer Surveillance Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18:2822-2828
2. Ellis IO: Impact of a national external quality assessment scheme for breast pathology in the UK. *J Clin Pathol*. 2006;59:138-45.

Risk of Breast Cancer after Atypical Hyperplasia (ADH, ALH) (7/22)

Further information:

Women have an enhanced breast cancer risk after ADH: one lesion RR 3.88 (95%CI 3.00-4.94), three lesions RR10.35 (95%CI 6.13-16.4). Less than 45 years at diagnosis of ADH RR 6.78 (95%CI 3.24-12.4) [2].

References:

1. Degnim A: Stratification of breast cancer risk in women with atypia: A Mayo Cohort Study. JCO 2007; 25(19):2671-2677

Strategy after Diagnosis of ADH (8/22)

Further information:

Significant histologic predictors of upgrade from ADH to carcinoma included number of terminal duct-lobular units (TDLU; >2) involved ($P = .0306$), presence of significant cytologic atypia suspicious for intermediate or high-grade carcinoma ($P < .0001$), and necrosis ($P = .0006$). Therefore, ADH lesions with significant cytologic atypia and/or necrosis are most likely to be associated with carcinoma and should be excised. ADH without these features, regardless of extent of involvement, and with complete removal of the targeted calcifications, is associated with a minimal risk (<3%) of carcinoma and may undergo mammographic follow-up only (Nguyen CV 2010, Allison KH 2010). Radiological calcification with suspicious or malignant characteristics and histological B3 with evidence of epithelial atypia has the highest positive predictive value (50%) (Rhaka et al. 2010). Even in the case of complete removal of microcalcifications there is a risk of 5 % of underestimation of malignancy (Penco 2010). An open excisional is recommended with exception of very small lesions (≤ 2 TDLU) and minimal atypia and complete removed imaging abnormality.

ADH in core- / vacuum-assisted biopsy (LoE 3a)

ADH at margins in resection specimen (LoE 3a)

References:

1. Nguyen CV: Atypical Ductal Hyperplasia in Directional Vacuum-Assisted Biopsy of Breast Microcalcifications: Considerations for Surgical Excision. Ann Surg Oncol. 2010 Oct 23. [Epub ahead of print]
2. Allison KH: Atypical ductal hyperplasia on vacuum-assisted breast biopsy: suspicion for ductal carcinoma in situ can stratify patients at high risk for upgrade. Hum Pathol. 2011 Jan;42(1):41-50
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10. Arora S: Atypical ductal hyperplasia at margin of breast biopsy - Is Re-excision indicated? *Ann Surg Oncol* 2007; 15(3):843-847

Lobular Intraepithelial Neoplasia (LIN) (9/22)

Further information:

Lobular neoplasia (LN) or lobular intraepithelial neoplasia (LIN) are the preferred terms for early neoplasia with lobular phenotype and include atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). For a long time, LN was considered to be just as a risk indicator and not a precursor lesion for the subsequent development of carcinoma. More recently, because of pathological and molecular studies, it is now believed that lobular neoplasia indeed is a non-obligatory precursor of invasive carcinoma, and at the same time a risk lesion for ipsi- and contralateral disease. Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, florid LCIS and pleomorphic LCIS were shown to behave more aggressively compared to classical lobular neoplasia. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. After diagnosis of LIN on core needle, or on vacuum-assisted biopsy, the average upgrade rate is about 15%. The management of lobular neoplasia in excisional biopsies by the pathologist requires attention to the following points: 1) He should be aware of the risk of occult microinvasion and pay attention to the careful workup of the specimen. 2) In cases of pleomorphic LCIS attention must be paid to the margin status like in low-grade DCIS, to make sure that florid or pleomorphic LN has been completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis or LIN with extensive involvement of lobules are not fulfilled which qualify for B5a. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.

References:

1. Contreras A: Lobular Neoplasia of the breast: An update. Arch Pathol Lab Med 2009; 133(7):1116-1120
2. Pinder S: Lobular in situ neoplasia and columnar cell lesions: diagnosis in breast core biopsies and implications for management. Pathology 2007, 39:208-216.
3. Lakhani I: The management of lobular carcinoma in situ (LCIS). Is LCIS the same as ductal carcinoma in situ (DCIS)? Eur J Cancer 2006; 42:2205-2211
4. Arpino G:: Lobular neoplasia on core-needle biopsy: clinical significance. Cancer 2004, 101:242-250

Statement: Indicator-/ precursor lesion

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Variants of Lobular Neoplasia (10/22) and Lobular Neoplasia with High Risk (11/22)

Further information:

Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, pleomorphic lobular carcinoma in situ (pLCIS) was shown to behave more aggressively compared to classical lobular neoplasia [1]. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. In this respect pLCIS mimics ductal carcinoma in situ (DCIS), but characteristically it is associated with classical LN and not with DCIS. Also, molecular profiling studies have shown that pLCIS is similar to classical LN, supporting its role as a special form of lobular neoplasia. As another approach for risk assessment, a classification of lobular neoplasia into three different grades of severity has been proposed, based on the extent of lobular cancerization [2]. The most severe grade (LIN 3) is called florid lobular carcinoma in situ nowadays [3]. It may be associated with microinvasion [4].

References:

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2. Bratthauer GL, Tavassoli FA. Lobular intraepithelial neoplasia: previously unexplored aspects assessed in 775 cases and their clinical implications. *Virchows Arch*. 2002;440(2):134-138.
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carcinoma in situ. Hum Pathol. 2013;44(10):1998-2009.

4. Ross DS, Hoda SA. Microinvasive (T1mic) lobular carcinoma of the breast: clinicopathologic profile of 16 cases. The American journal of surgical pathology. 2011 May;35(5):750–6.

Strategy after Diagnosis of LIN (12/22)

Further information:

In contrast to atypical ductal hyperplasia, it is less clear if a follow-up excisional biopsy is beneficial to the outcome of a patient with the finding of lobular neoplasia in the core biopsy, and therefore there is some disagreement if excision should be recommended as a rule or not. This is mainly due to the relative infrequency of lobular neoplasia as the most severe finding in core biopsies and the even lower number of excisional biopsies in this situation. Not surprisingly these small studies have led to widely discrepant results and conflicting interpretations of published data. An excisional biopsy was recommended in fully developed LCIS because of an upgrade rate of greater than of 25% [1] or 16% [2], but results were inconclusive with lesions of lesser extent, namely atypical lobular hyperplasia. The argument against a routine follow-up biopsy is that LN as the most significant pathology usually is an incidental finding in an otherwise benign core biopsy and if there is no other clinical or radiological detectable lesion, it is unlikely that an excisional biopsy could yield anything more significant [3]. This argument has to be taken seriously, and at least all cases with LCIS and a mass lesion should be followed up by a surgical biopsy. However, because of the reported upgrade rates in fully developed LCIS, the nature of these lesions as non-obligate precursors, and risk of missing a radiologically occult invasive cancer, an open biopsy in classical LCIS should be considered as an option also [2], especially if multiple lobules are involved [4-6].

References:

LIN in core- / vacuum-assisted biopsy (LoE 2b)

1. Shin SJ, Rosen PP. Excisional biopsy should be performed if lobular carcinoma in situ is seen on needle core biopsy. Arch Pathol Lab Med. 2002 May 31;126(6):697–701.

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LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a)

1. Ciocca R: Presence of lobular carcinoma in situ does not increase recurrence in patients treated with breast-conserving therapy. *Ann Surg Oncol* 2008; 15:2263-2271

Flat Epithelial Atypia (FEA) (13/22)

Further information:

FEA represents one of the earliest morphologically recognizable neoplastic alterations of the breast. It is characterized by mildly to severely atypical cells simply replacing the single layer of native epithelial cells in a flat fashion without appreciable proliferation.

Marker Lesion

FEA is highly associated with microcalcification (77%). The mammographic features are amorphous and pleomorphic microcalcification. In about one-third to one-quarter of cases of FEA seen at core biopsy, a more advanced lesion is found at excision: ADH, DCIS and tubular carcinoma. A 2- to 3-fold increase in the occurrence of ADH in the presence of FEA versus in their absence ($P < .005$) was observed. A finding of FEA on benign breast biopsy may indicate the presence of ADH, a more worrisome lesion (Boulos FI). FEA might be associated with noninvasive cancer but not with invasive cancer.

References:

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2. Moinfar F. Flat ductal intraepithelial neoplasia of the breast: A review of diagnostic criteria, differential diagnoses, molecular-genetic findings, and clinical relevance - It is time to appreciate the Azzopardi concept! Arch Pathol Lab Med 2009; 133(6):879-892.
3. Böcker W: Flache epitheliale Atypie. Pathologe 2009; 30:36-41.

Statement: Marker Lesion (LoE 3b)

1. Kunju L: Significance of flat epithelial atypia on mammotome core needle biopsy:should it be excised? Hum Pathol 2006; 38:35-41
2. Noske A: Flat eoithelial atypia is a common subtyp of B3 breast lesions and associated with noninvasive cancer but not with invasive cancer in final excision histology. Hum Pathol 2009; Epub ahead of print.
3. Pandey S: Columnar Cell Lesions of the Breast: Mammographic Findings with Histopathologic Correlation. Radiographics 2007; 27(suppl_1):S79-S89
4. Collins L: Clinical and pathological features of ductal carcinoma in situ associated with the presence of flat epithelial atypia: an analysis of 543 patients. Modern Pathology 2007; 20:1149-1155
5. Boulos F: Histologic Associations and long-term cancer risk in columnar cell lesions of the breast. Cancer 2008; 113:2415-2421

Strategy after Diagnosis of FEA (14/22)

Further information:

If a FEA is detected in core biopsy further no further (open) biopsy is indicated if the underlying lesion / calcification is completely removed (Lee TJ, 2010). In cases of FEA combined with an ADH further surgery depends on the ADH lesion (Ingegnoli A, 2010).

Statement: FEA in core (LoE 3a)

Statement: FEA at margins in resection specimens (LoE 3b)

References:

1. Lee TY: Flat epithelial atypia on breast needle core biopsy: a retrospective study with clinical-pathological correlation. Breast J. 2010 Jul-Aug;16(4):377-83
2. Ingegnoli A: Flat epithelial atypia and atypical ductal hyperplasia: carcinoma underestimation rate. Breast J. 2010 Jan-Feb;16(1):55-9.
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5. David N: Diagnosis of flat epithelial atypia (FEA) after stereotactic vacuum-assisted biopsy (VAB) of the breast: what is the best management - systematic surgery for all or follow-up? J Radiol 2006, 87:1671-1677.
6. Collins L: Clinical and pathological features of ductal carcinoma in situ associated with the presence of flat epithelial atypia: an analysis of 543 patients. Modern Pathology 2007, 20:1149-1155.

Papilloma (15/22)

Further information:

Benign intraductal papillomas occur either as a central papilloma originating from the ducts in the subareolar region, or peripherally, and both locations can be either solitary or multiple. Both central and peripheral papillomas are characterized by fibrovascular cores with epithelial and myoepithelial cell layers. Central intraductal papillomas with a predominant or exclusive glandular differentiation are called ductal adenoma [1]. Intraductal papillomas and ductal adenomas may show regressive changes, such as sclerosis or infarction, also also epithelial or myoepithelial hyperplasia or squamous or apocrine metaplasia. These changes may cause diagnostic difficulties in core needle biopsy [2]. The term papillomatosis is not used in the WHO classification of the breast, because was historically used both for usual type ductal hyperplasia and for papillomas.

Atypical epithelial proliferations (ADH and DCIS) may occur in papillomas, and are usually of low grade. As with atypical intraductal proliferative lesions, the distinction of ADH and DCIS within a papilloma rests with quantitative criteria [1]. An intraductal papilloma with ADH is diagnosed when the atypical epithelial proliferation is < 3 mm, while larger atypical epithelial proliferations within a papilloma fulfill the criteria of an intraductal papilloma with low grade [3]. This definition replaces alternative terminologies that were focussed on the proportion of atypical cells (30% or 90%) within a papilloma. An intermediate or high grade DCIS within a papilloma can be diagnosed regardless of the extent of atypia.

References:

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2. Bilous M. Breast core needle biopsy: issues and controversies. Mod Pathol. 2010 May 1;23 Suppl 2:S36–45.

3. Page DL, Salhany KE, Jensen RA, Dupont WD. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. *Cancer*. 1996 Jul 14;78(2):258–66.

Strategy after Diagnosis of Central Papilloma (16/22)

Further information:

A policy of open excisional biopsy after the diagnosis of a central papilloma has been recommended by the European guidelines for quality assurance in breast cancer screening [1]. However, this recommendation is still controversial [1, 2]. The finding of an ADH or DCIS in a papilloma has similar therapeutic consequences, provided the surrounding transition system is free of DCIS. In both cases, complete excision of the lesion without subsequent radiotherapy [4] is sufficient. For this reason, the distinction between ADH and DCIS in a papilloma is rejected by some authors [4].

References:

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2. Wen X, Cheng W. Nonmalignant Breast Papillary Lesions at Core-Needle Biopsy: A Meta-analysis of Underestimation and Influencing Factors. *Ann Surg Oncol*. 2012 Aug 10;20(1):94–101.
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4. Collins L, Schnitt S. Papillary lesions of the breast: selected diagnostic and management issues. *Histopathology*. 2008;52(1):20–9.

Radially Sclerosing Lesion (17/22)

No further information

No references

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (18/22)

No further information

No references

Follow-up Imaging for Women Age 50-69 Years with B3-Lesions (19/22)

Further information:

Women with ADH and LIN need to be informed about their elevated risk for breast cancer. Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolute terms, helping women to make an informed decision to her personal needs and values. Atypia patients who drank alcohol and had a first-degree relative with breast cancer have an increased risk of breast cancer compared to those without atypia [1].

References:

1. Whiffen A: Predictors of Breast Cancer Development in Women with Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia. Ann Surg Oncol. 2010 Sep 28. [Epub ahead of print]
2. Weir R: Risk factors for breast cancer in women:a systematic review of the literature. Christchurch: New Zealand Health Technology Assessment (NZHTA); 2007.
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4. Degnim A: Stratification of breast cancer risk in women with atypia: A Mayo Cohort Study. JCO 2007; 25(19):2671-2677.
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München: Zuckschwerdt Verlag, 2008.

7. NCCN, National Comprehensive Cancer Network: Breast cancer screening and diagnosis V.1.2010, ed 2010. USA, NCCN, 2010
8. O'Connor A: Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-35

Medical Prevention for Women at Increased Risk (including Women with LIN and ADH) (20/22)

Further information:

Studies on medical prevention for women at increased risk include women with LIN and ADH.

References:

1. Whiffen A: Predictors of Breast Cancer Development in Women with Atypical Ductal Hyperplasia and Atypical Lobular Hyperplasia. *Ann Surg Oncol*. 2010 Sep 28
2. Visvanathan K: American Society of Clinical Oncology Clinical Practice Guideline: Update on the use of pharmacologic interventions including tamoxifen, raloxifen and aromatase inhibition for breast cancer risk reduction. *JCO* 2009; 27:3235-3258
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6. Vogel V: Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial. *JAMA* 2006; 295(23):2727-2741.
7. Fischer B: Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. *J Natl Cancer Inst* 2005; 97:1652-1662
8. IBIS-II International Breast Cancer Intervention Study <http://www.ibis-trials.org>

Outcome of Medical Prevention (1) (21/22)

No further information

References:

1. Visvanathan K: American Society of Clinical Oncology Clinical Practice Guideline: Update on the use of pharmacologic interventions including tamoxifen, raloxifen and aromatase inhibition for breast cancer risk reduction. JCO 2009; 27:3235-3258
2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized INIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. Vogel V: Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial. JAMA 2006; 295(23):2727-2741.
4. Fischer B: Tamoxifen for the prevention of breast cancer: current status of the national surgical adjuvant breast and bowel project P-1 study. J Natl Cancer Inst 2005, 97:1652-1662

Outcome of Medical Prevention (2) (22/22)

Further information:

Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolute terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

References:

1. Visvanathan K.: American Society of Clinical Oncology Clinical Practice Guideline: Update on the use of pharmacologic interventions including tamoxifen, raloxifen and aromatase inhibition for breast cancer risk reduction. JCO 2009; 27:3235-3258
2. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized INIS-I trial. J Natl Cancer Inst 2007; 99:272-282
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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Ductal Carcinoma in Situ (DCIS)

Ductal Carcinoma in Situ DCIS

- **Version 2002:**
Gerber
- **Versions 2003–2013:**
**Audretsch / Brunnert / Costa / Fersis /
Friedrich / Hanf / Junkermann / Lux /
Maass / Möbus / Nitz / Oberhoff / Scharl /
Souchon / Thomssen**
- **Version 2014:**
Thill / Solomayer

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Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

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- **Mammography**
 - Magnification view of microcalcification
 - Increase of detection rate of G1/G2 DCIS by full-field digital mammography (versus screen-film)
- **Stereotactic core needle / vacuum biopsy (VAB)**
 - Specimen radiography
 - Marker (Clip) left at biopsy site for location if lesion is completely removed
- **Assessment of extension**
 - MRI
- **Clinical examination**
- **FNA / ductal lavage**
- **Interdisciplinary board presentation**

**Oxford / AGO
LoE / GR**

1b A ++

4 C ++

2b B +

2b B ++

2b B ++

5 D ++

3a C +/-

5 D ++

5 D -

5 D ++

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Surgical Treatment for Histologically Proven DCIS I

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|------------|
| ➤ Excisional biopsy (wire guided) | 2b | B | ++ |
| ➤ Bracketing wire localization in large lesions | 5 | D | + |
| ➤ Specimen radiography | 2b | B | ++ |
| ➤ Intraoperative ultrasound (visible lesion) | 3a | C | +/- |
| ➤ Immediate re-excision for close margins (specimen radiography) | 1c | B | ++ |
| ➤ Intraoperative frozen section | 5 | D | -- |
| ➤ Interdisciplinary board presentation | 2b | C | ++ |

Open biopsy in suspicious lesions (mammographical microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided

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Surgical Treatment for Histologically Proven DCIS II

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| | | | Oxford / AGO LoE / GR | | |
|---|---|--|--------------------------|---|-----|
| | | | 2b | C | ++ |
| ➤ | Histologically clear margins (R0) | | 2b | C | ++ |
| ➤ | Multifocal DCIS: BCT if feasible (incl. RT) | | 2b | B | + |
| ➤ | Re-excision required for close margin ≤ 2 mm in paraffin section) | | 2b | C | + |
| ➤ | Mastectomy* | | | | |
| | ➤ Large lesions confirmed by multiple biopsies; no clear margins after re-excision | | 2a | B | ++ |
| ➤ | SNE* | | 3b | B | + |
| | ➤ Mastectomy | | 3b | B | + |
| | ➤ In case of DCIS in the male breast | | 5 | D | + |
| | ➤ BCT: ≥ 5 cm or ≥ 2.5 cm + high nuclear grade/ comedonecrosis | | 3b | B | +/- |
| ➤ | ALND | | 2b | B | - - |

* Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.

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DCIS – Prognostic Factors for the Incidence of Local- / Locoregional Recurrence

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- **Resection margins**
- **Residual tumor-associated microcalcification**
- **Age**
- **Size**
- **Grading**
- **Comedo necrosis**
- **Architecture**
- **Method of diagnosis**
- **Focality**
- **(mod.) Van Nuys Prognostic Index**
- **Palpable DCIS**
- **Palpable + COX-2+, p16+, Ki-67+**
- **Palpable + ER-, HER2+, Ki-67+**
- **HER2/neu (positive vs. negative)**
- **ER/PgR (positive vs. negative)**
- **DCIS-Score**
- **DCIS with microinvasion – treatment in analogy to invasive breast cancer**
- **Intrinsic subtypes (luminal A, B, HER2+, triple negative)**

Oxford / AGO LoE / GR

| | | |
|----|---|-----|
| 1a | A | ++ |
| 2b | C | ++ |
| 1a | A | ++ |
| 1a | A | ++ |
| 1a | A | ++ |
| 1a | A | ++ |
| 2b | C | + |
| 1a | A | ++ |
| 1a | A | ++ |
| 2b | C | +/- |
| 2b | C | +/- |
| 2b | C | +/- |
| 1a | B | +/- |
| 1a | B | +/- |
| 2c | C | +/- |
| 3b | C | ++ |
| 2b | C | - |

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DCIS Radiotherapy

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Radiotherapy after:

- Breast conserving surgery (BCS)
- Mastectomy

Modality:

- Partial breast radiotherapy (PBI)
- Hypofractionated radiotherapy regimens
- Radiotherapy boost on the tumor bed
 - Women younger than 45-50 years

1a A ++

2b B --

3a D --

2b D -/+*

2b D --

2b C +/-

Side effects and disadvantages of radiotherapy must be balanced against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of “good risk” patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases.

* Analysis in ongoing trials

Cochrane Analysis

Radiation after Surgery (all/with Radiation after Breast Conserving Surgery)

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Goodwin A, Parker S, Gherzi D, Wilcken N.

Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev. 2013 Nov 21;11:CD000563. doi: 10.1002/14651858.CD000563.pub7.

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References

DCIS Postoperative Systemic Treatment

**Oxford / AGO
LoE / GR**

- **Tamoxifen (only ER+)**
 - AI if postmenopausal and
contraindication against tamoxifen
- **Other endocrine options**
- **Trastuzumab (only HER2+)**

| | | |
|-----------|----------|-------------|
| 1a | A | + |
| 5 | D | +/-* |
| 5 | D | -* |
| 5 | D | -- |

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Cochrane Analysis

Tamoxifen after DCIS (all/with Radiation)

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Staley H, McCallum I, Bruce J.

Postoperative tamoxifen for ductal carcinoma in situ.

**Cochrane Database Syst Rev. 2012 Oct 17;10:CD007847. doi:
10.1002/14651858.CD007847.pub2.**

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Local Recurrence of DCIS after Tumorectomy w/o Irradiation

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| | Oxford / AGO LoE / GR |
|--|--------------------------|
| ➤ MRI (follow-up after history of LCIS) | 2b B +/- |
| ➤ Simple mastectomy | 3a C ++ |
| ➤ Secondary tumorectomy leads to recurrence rates about 30% (NSABP B17) | 5 D +/- |
| ➤ Plus radiotherapy (in case of no previous RT) | 3 C ++ |

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Prognosis for invasive recurrence seems to be better than in case of primary invasive breast cancer; ~ 50% of recurrences are invasive.

Key Points

- **DCIS is a local disease and should primarily be treated with local approaches only**
- **Addition of Tamoxifen to radiotherapy reduces risk of local recurrence (LoE 1a)**
- **BCT offers an acceptable local control rate for many patients with DCIS (LoE 1a)**
- **After BCS, postoperative radiotherapy is recommended (LoE 1a)**
- **So far, no influence on survival by postoperative radiotherapy can be detected (LoE 1a)**
- **Young age is an independent risk factor for local recurrence (LoE 1a). Therefore, especially younger patients might benefit from a boost irradiation (LoE 2b)**
- **As margins are an important prognostic factor for local tumor control, R0-resection should be achieved (LoE 1b)**
- **So far, no patients' subset has been identified that not benefit from radiotherapy after BCS in terms of improved local tumor control (LoE 1a)**
- **Hypofractionated radiotherapy might be as safe and effective as standard RT; wait for results of ongoing RCT.**

Ductal Carcinoma in Situ (DCIS) (2/12)

Further information:

Scientific data source screened (for preparation of the current version):

Systematic review of published evidence for 2014-Version:

| | |
|--------|------|
| PUBMED | 2013 |
| ASCO | 2013 |
| SABCS | 2013 |

Screened guidelines: NCCN – Clinical Practice Guidelines in Oncology – Breast cancer: V.3.2013; DEGRO 2007-2012; International Society Geriatric Oncology; Consensus on the primary therapy of early breast cancer (St. Gallen 2013); S3-Guideline of the German Cancer Society 2012; NICE (UK) Clinical Guidelines 2009-2011; Guidelines for clinical practice from French expert review board of Nice/Saint-Paul de Vence; French national guidelines 2011/2012; National Cancer Institute (USA) 2010; Scottish Intercollegiate Guidelines Network (SIGN) 2010; New Zealand Guidelines Group (NZGG) 2009-2010; National Health and Medical Research Council (NHMRC Australia) 2010; Belgian Health Care Knowledge Centre (KCE) 2010; Guidelines International Network (G-I-N) 2010; British Medical Journal (BMJ) clinical guidelines (2009-2010); International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) 2012, ESMO Guidelines 2011.

No references

Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/12)

Further information:

Regarding the pretherapeutic assessment of suspicious lesions (BIRADS IV) the stereotactic sore needle or the vacuum biopsy is recommended. If the lesion is completely removed by the biopsy, a marker clip should be left at the biopsy for the exact location of the lesion.

Moreover, clinical examination should be performed.

A further prospective observational study presented that the presence of DCIS significantly affects the accuracy of measuring the sizes of malignant breast tumors when using either B-mode sonography or real time elastography [Soliman et al., 2012].

The actual literature shows concordantly, that MRI is better than mammography for discriminating the exact size of DCIS especially for high grade lesions. On the other hand there is the risk of overestimating benign lesions with the consequence of consecutive interventions. DCIS is not a lethal disease and therefore the cost-risk relations have to be considered carefully. Because of this the AGO recommends +/-.

Regarding early cancer detection, full-field digital mammography has a higher detection rate of low- and intermediate-grade DCIS compared to screen-film mammography [Nederend et al., 2012].

References:

Kim do, Y., W. K. Moon, et al. (2007). "MRI of the breast for the detection and assessment of the size of ductal carcinoma in situ." Korean J Radiol 8(1): 32-39.

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Surgical Treatment for Histologically Proven DCIS I (4/12)

Further information

New 2014

Ahmed and Douek published a systematic review and a metaanalysis to evaluate the impact of intra-operative ultrasound (IOUS) in comparison to wire-guided localization (WGL) in non-palpable breast cancers and DCIS.

Studies were considered eligible for inclusion in this systematic review if they (1) assessed the role of surgeon-performed IOUS for the treatment of non-palpable breast cancers and ductal carcinoma in situ (DCIS) and (2) specified surgical margin excision status. Those studies, which were randomized controlled trials (RCTs) or cohort studies with comparison WGL groups were included in the meta-analysis. For those studies included in the meta-analysis, pooled odds ratios (ORs) and 95 % confidence intervals (CIs) were estimated using fixed-effects analyses and random-effects analyses in case of statistically significant heterogeneity ($p < 0.05$).

Eighteen studies reported data on IOUS in 1,328 patients with non-palpable breast cancer and DCIS. Nine cohort studies with control WGL groups and one RCT were included in the meta-analysis. Successful localization rates varied between 95 and 100 % in all studies and there was a statistically significant difference in the rates of involved surgical margins in favour of IOUS with pooled OR 0.52 (95 % CI 0.38-0.71).

The authors concluded that compared with WGL, IOUS reduced involved surgical margin rates in non-palpable lesions as long as they are visible. For invisible DCIS and EIC IUOS can not be recommended.

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Surgical Treatment for Histologically Proven DCIS II (5/12)

Further information:

Dunne et. al. have evaluated the risk of recurrence in dependence of the tumorfree margins. They demonstrated that free margins of 5 mm and more have no significant advantages compared with free margins of at least 2 mm. The clinical recommendation has to be seen in the way that at DCIS tumorfree margins of 2 – 5 mm are enough, while for tumorfree margins of less than 2 mm a re-excision should be recommended.

Planning the surgery it should be recognized that patients who present a palpable mass in case of DCIS have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.

The indication for SLNE at DCIS should be discussed: there is no question that in case of mastectomy a SLNE should be performed, because a SLNE after mastectomy is not feasible and an axillary dissection had to be done. The recommendation for large DCIS (> 5cm) or DCIS \geq 2.5 cm with high-grade and/or comedonecrosis is similar.

DCIS in male patients should be treated with mastectomy and SNE.

New data with small patient numbers show that intraoperative evaluation of margins by radiofrequency spectroscopy seems to be promising.

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DCIS – Prognostic Factors for the Incidence of Local- /Locoregional Recurrence (6/12)

Further information:

With the help of the Van Nuys Prognostic Index – one of seven scores -, that is based on retrospective data analysis and that grading, tumor size, tumor free margins and age, it was tried to work out standard treatment recommendations. Nevertheless some studies demonstrated high recurrence rates in patients with low risk DCIS possibly based on the heterogeneous morphology.

In the EORTC-Study 10853 with 863 patients age (\leq 40 years), method of diagnosis (mammography, palpable lesion), tumorfree margins (free/not free/ unclear), grading, architecture (clinging/cribriforme and clinging/solide, comedonecrosis) as well therapy (tumorectomy+/-radiotherapy) are independent prognostic factors for local and locoregional recurrence in multivariate. The metaanalysis of Wang (2011) demonstrated, that comedonecrosis, focality, tumorfree margins, method of detection, grading and tumor size are independent predictors for local recurrences.

Regarding the age, the Italian Radiation Oncology Group performed a multi-institutional study of conservative treatment of DCIS [Vidali et al., 2012]. The trial was characterized by a very long median follow-up (> 11 years). Age was a statistically significant prognostic factor ($p=0.0009$).

In the years 2010 und 2011 another two scores, that are based on morphological criteria and age, were published. At the moment there are no well evaluated prognostic factors in the area of molecular markers, molecular profiles, DNA methylating processes, a.s.o. Kerlikowske et al. have evaluated a molecular profile by Cox-2+ki67+p16+ and ER-HER2+Ki-67+ expression combined with palpability of the lesions, that was associated with a higher risk for invasive recurrences but not for non invasive recurrences. DCIS-Score from Solin could be a helpful tool in the future.

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DCIS Radiotherapy (7/12)

Further information:

A randomized controlled clinical trial comparing mastectomy alone with local excision by BCS consisting of removal of the DCIS to clear margins (regarding “clear margins” see also editorial by Morrow M, Katz SJ 2012) followed by radiation therapy has not been done. Nevertheless, the available data suggest that long-term survival is similar with both therapeutic approaches providing excellent outcomes.

After mastectomy for pure DCIS the rates of local or regional relapses are very low (<2%) independently of patient's age (Ho A et al. Breast 2011). Thus, postmastectomy radiotherapy (PMRT) is not recommended. Even with positive or close mastectomy margins, the rates of chest wall recurrences were so low that PMRT is likely not warranted (Chadha M et al. Int J Surg Oncol 2012;2012:423520. doi: 10.1155/2012/423520. Epub 2012 Jun 13; Childs SK, Int J Radiat Oncol Biol Phys 2012 Sep 10. doi:pii: S0360-3016(12)03334-2. 10.1016/j.ijrobp.2012.07.2377. [Epub ahead of print]).

Because of the data of EORTC- and NSABP B-17 studies the radiotherapy of DCIS after BCS has to be seen as standard by reducing the local recurrence rate significantly (Julien JP Lancet 2000; 355: 528-533; Fisher B J Clin Oncol 1998; 16: 441-452; Solin LJ 2012). In small lesions of DCIS with tumor size smaller than 2 cm – 3 cm, tumorfree margins greater than ≥ 10 mm and low or intermediate grading and VNPI ≤ 4 side effects and disadvantages of radiotherapy in relation to risk reduction of local recurrences should be discussed (Schwartz et al. Hum Path 2000)

The data of radiotherapy after BCS in newer studies have confirmed these results. The subgroup of patients who do not benefit from radiotherapy might be very small. A clear subgroup that does not benefit from radiotherapy cannot be defined at the moment (Shaitelman SF et al. 2012). Therefore the interdisciplinary tumor conference is of main importance (Bijker et.al. (EORTC) J.Clin Oncol, 2006).

With respect to retrospective studies nor small tumors nor larger tumor free margins nor a differentiation with histological criterias nor the Van Nuys PI allow to omit the radiotherapy.

Die EBCTCG (2010) has analysed the of 4 randomised studies concerning radiotherapy after BCS for DCIS and could demonstrate that an absolute reduced 10 years risk for recurrences of 15,2% for invasive recurrences with a higher reduction in elder patients independently from other prognostic factors. A prospective study of ECOG (ECOG 5194) without radiotherapy in patients with lesions < 2,5 cm + low-intermediate grade and high grade lesions < 1 cm (RR> 3mm) showed after a FU of 5 years 6,1 % and 15,3% ipsilateral breast events.

Possibly a huge part of recurrences in the low risk group will appear in later times so that the omission of radiotherapy after BCS has to be indicated carefully (Shaitelman SF et al. 2012). The partial breast irradiation for DCIS is experimental at that time; in small groups 5 year recurrence rates of 3,39% are described. Data published in Lancet Oncology 2011 with a FU of 12,7 months demonstrated a reduction of ipsilateral local recurrences after BCS and radiotherapy of 68% for invasive lesions and of 62 % of non-invasive lesions (UK-trial). Wapnir et al. published in JNCI 2011 a cumulative 15-years breast cancer mortality after lumpectomy of 3,1%, after BCS and radiotherapy of 4,7% and after BCS and radiotherapy and Tamoxifen of 2,7%. There is no valid data for the use of AI (anastrozole, etc.).

Actual unanswered questions and study endpoints of actual randomized clinical trials regarding the impact of radiation therapy treatment of DCIS are:

1. RT beneficial even for patients with “good risk”-criteria (RT=G 9804; McCormick et al. 2012)?
2. Isoeffectiveness of different fractionation schedules (hypofractionation versus standard fractionation (TROC 07.01; Bonbis-Trial; ANZCTR.org; Azria et al. 2008; Wai et al. 2011; Riou et al. 2012)?
3. Additional benefit by boost irradiation of the tumor bed following BCS and WBI (TROC 07.01; Bonbis-Trial; ANZCTR.org; Azria et al. 2008; Wai et al. 2011; Riou et al. 2012)?
4. Non-inferiority and/or equieffectiveness of whole breast irradiation (WBI) with accelerated partial breast irradiation (APBI) (E5194-Studie, NSABP B-39-trial; National Cancer Institute website. NSABP B-39; Goyal et al. 2011; Jeruss et al. 2011; Park et al. 2011)?
5. Impact of trastuzumab given concurrently with irradiation for patients with HER2+ DCIS resected by lumpectomy (NSABP B-43-trial; Cobleigh MA et al. 2012)?

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Cochrane Analysis post-operative radiotherapy (8/12)

No further information

No references

DCIS Postoperative Systemic Treatment (9/12)

Further information:

The NSABP B24-Studie showed a risk reduction of ipsilateral non invasive recurrences of 18% (and contralateral of 78%) and of ipsilateral invasive recurrences of 44% (contralateral of 37%) at a median FU 74 months independently of ER-status (Fisher B Lancet 1999; 353: 1993-2000). This is confirmed by the data of the UK-trial from 2010. In San Antonio 2002 data had been presented that showed a significant reduction of all breast cancer events by 59% in ER-positive non invasive BC, while in ER-negative non invasive breast cancers the recurrence rate was reduced not significantly by 20% (Allred DC Breast Cancer Research and Treatment Vol 76 Suppl 1 Dec 2002: abstract 30). Wapnir et al. published in JNCI 2011 a cumulative 15-years breast cancer mortality after lumpectomy of 3.1%, after BCS and radiotherapy of 4.7% and after BCS and radiotherapy and Tamoxifen of 2.7%. There are no valid datas for the use of AI (anastrozole, etc.). Study participation is recommended.

New 2013

Regarding the use of tamoxifen after DCIS, a Cochrane meta-analysis was published in 2012 [Staley et al., 2012]. Two randomized controlled trials were included involving 3375 women. Tamoxifen after surgery for DCIS reduced recurrence of both ipsilateral (same side) DCIS (HR 0.75; 95% CI 0.61 to 0.92) and contralateral (opposite side) DCIS (RR 0.50; 95% CI 0.28 to 0.87). There was a trend towards decreased ipsilateral invasive cancer (HR 0.79; 95% CI 0.62 to 1.01) and reduced contralateral invasive cancer (RR 0.57; 95% CI 0.39 to 0.83). The number needed to treat in order for tamoxifen to have a protective effect against all breast events is 15. No reliable number needed to treat to harm could be calculated. Moreover, it was not clear how patient characteristics (e.g. menopausal status, age and tumour ERstatus) affect or predict response to tamoxifen. There was no evidence of a difference detected in all cause mortality (RR 1.11; 95% CI 0.89 to 1.39).

The impact of trastuzumab given concurrently with radiation therapy (RT) to RT alone for patients with HER2+ DCIS resected by lumpectomy is actually proven in a phase III clinical trial by the NSABP (NSABP B-43; Cobleigh MA et al. 2012).

New in 2014

The NSABP B-43 trial is fully recruited. 5,645/5,861 had analyzable blocks; only 1,969 (34.9 %) were HER2 positive, lower than previously reported. A total of 1,428 patients have been accrued, 1,137 (79.6 %) of whom have follow-up information. The average follow-up time for the 1,137 patients is 23.3 months. No grade 4 or 5 toxicity has been observed. No trastuzumab-related safety signals have been observed. Other data from this trial will be awaited.

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New 2013

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Cochrane Analysis Tamoxifen after DCIS (10/12)

No further information

No references

Local Recurrence of DCIS after Tumorectomy w/o Irradiation (11/12)

Further information:

Surveillance of patients with DCIS should be performed similar to patients with invasive breast cancer. Regarding LCIS (LIN III) a retrospective review of 670 screening breast MR studies was performed between January 2003 and September 2008. 220 women with a history of LCIS were integrated [Sung et al., 2012]. The median follow-up of screening was 3 years (0.5-5 years). MR imaging was a useful adjunct modality for screening women with a history of LCIS at a high-risk of developing breast cancer, resulting in a 4.5% incremental cancer detection rate.

The treatment of choice of a locoregional recurrence after BCS and radiotherapy for DCIS is the salvage mastectomy especially on the basis that 50% of the recurrences are invasive and half of them were diagnosed in an unfavourable stage (Silverstein MJ J Clin Oncol 1998; 16:1367-1373). A second BCS is combined with a local recurrence rate of 30% (Fisher B et al. Cancer 1999; 86:429-438). At the moment there only is a low level of evidence for the mastectomy after local recurrence of a DCIS. There are no valid datas whether a second BCS is aequieffective with mastectomy and whether the prognosis of an invasive recurrence is better than the one of primary breast cancer.

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Key Points (12/12)

No further information

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New 2013

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Recommended clinical Trial:

IBIS 2

Adjuvant Tamoxifen Compared With Anastrozole in Treating Postmenopausal Women With Ductal Carcinoma In Situ

<http://www.clinicaltrials.gov/ct2/show/NCT00072462?term=dcis&rank=12>

<http://www.gabg.de/studien/ibis2d.html>

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| GEC-ESTRO APBI TRIAL |
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Interstitial Brachytherapy Alone Versus External Beam Radiation Therapy After Breast Conserving Surgery for Low-Risk Invasive Carcinoma and Low-Risk Ductal Carcinoma in Situ (DCIS) of the Female Breast

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Rezai / Simon / Solomayer / Thomssen /
Untch**

➤ **Version 2014:**
Kühn / Kümmel

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Information

References

Pretherapeutic Assessment

**Oxford / AGO
LoE / GR**

➤ **Palpation**

5 D ++

➤ **Mammography**

2b B ++

➤ **Ultrasound (breast & axilla)**

2b B ++

➤ **Minimalinvasive biopsy****

1c A +

➤ **MRI***

1c B +/-

* No reduction of re-excision rate.

The possibility of MRI guided biopsy is the precondition of breast MRI (e.g. dense breast tissue and invasive lobular cancer , suspicion of multifocal or multicentric disease)

** If clinical examination, mammography, ultrasound and in some cases MRI are not able to determine the extension of lesion

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Perioperative Staging

**Oxford / AGO
LoE / GR**

- **History and physical examination**

5 D ++

High metastatic potential and / or symptoms:

- **Chest X-ray**

5 D +

- **Liver ultrasound**

5 D +

- **CT-scan**

5 D +

- **Bone-scan**

5 D +

- **FDG-PET or FDG-PET / CT**

4 C -

- **Whole body MRI**

4 C -

Evidence of Surgical Procedure

**Oxford / AGO
LoE / GR**

- **Survival rates after lumpectomy + XRT are equivalent to those after (modified) radical mastectomy** **1a A**
- **Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy** **1b A**
- **Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy** **2b B**
- **Conservation of the NAC (nipple areola complex) is an adequate surgical procedure in tumors of the periphery of the gland and after tumor-free section of retroareolar tissue** **4b C**

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Breast Conservation: Surgical Technical Aspects

Oxford / AGO LoE / GR

- **Non-palpable lesion**
 - Wire guided localisation 2b B ++
 - Radionuclide guided localisation 2b B +/-
 - Specimen radiography or ultrasound 2b B ++
- **Tumor-free margins required** 2a A ++
- **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)** 1c B ++
- **Re-excision required for involved margins (paraffin section)** 3b C +
- **Therapeutic stereotactic excision alone** 4 D - -
- **Ultrasound guided surgery to prevent re-excision** 1a A +/-

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Breast Conservation Surgery (BCS)

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- | | | | |
|---|-----------|----------|------------|
| ➤ Multicentricity | 2b | B | +/- |
| ➤ Positive microscopic margins after repeated excision | 2b | B | - - |
| ➤ Inflammatory breast cancer | 2b | B | - - |
| pCR after neoadjuvant chemotherapy | | | +/- |

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Axillary Lymph Node Dissection I

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Axillary lymph node dissection (≥ 10 LN)

- To improve survival
- For staging
- For local control

Axillary lymph node dissection:

- DCIS
- cT1 /2 cN0 (without prior sentinel)
- SN + (cT1/2 cN0; < 3 SN +, BCS + tangential radiation field, no subsequent axillary radiation, adequate systemic therapy)
- SN + (mic)
- SN (i+)
- SN + mastectomy

Axillary lymph node dissection indicated, but not feasible

- Radiation according to AMAROS-Trial

Oxford / AGO LoE / GR

| | | |
|----|---|-----|
| 3 | D | - |
| 3 | A | ++ |
| 2a | A | +/- |

| | | |
|----|---|----|
| 2b | B | -- |
| 1b | A | -- |

| | | |
|----|---|-----|
| 1a | B | +/- |
| 1b | A | - |
| 2b | B | -- |
| 1b | B | + |

| | | |
|-----------------|---|-----|
| 1b ^a | B | +/- |
|-----------------|---|-----|

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Surgical Treatment of Axillary Lymph Nodes pre and post NACT (Neoadjuvant Chemotherapy)

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| SLNB pre or post NACT - cN0 | | | | | | |
|---|--|------------------------------|--------------------|---------|--------|----------|
| SLNB pre NACT SLNB post NACT | | | | 2b 3 | B B | + +/- |
| Surgical Procedure according to lymph node status | | | | | | |
| cN-Status (prior Therapy) | pN-Status (prior Therapy) | cN-Status (after Therapy) | Surgical Porcedure | | | |
| cN0 | pN0(sn) | - | nihil | 1a | A | + |
| cN0 | pN+(sn) according ACOSOG Z11* criteria | ycN0 | ALND | 3 | B | +/- |
| cN0 | pN+(sn) <u>not</u> according to ACOSOG* criteria | ycN0 | ALND | 2b | B | + |
| cN+ | cN+ (CNB/FNA) | ycN0 | SNB ALND | 3 2b | B B | +/- + |
| | | ycN+ (CNB/FNA) | ALND | 2b | B | ++ |

* T1/T2, BCT, 1-2 SLN pos, Breast radiation

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Sentinel Lymph Node Excision (SNE): Indications I

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| | | | |
|--|----|---|-----|
| ➤ Clinically (cN0) / sonographically neg. axilla | 1b | A | ++ |
| ➤ T 1-2 | 2b | A | ++ |
| ➤ T 3, 4a-c | 3b | B | + |
| ➤ Multifocal / multicentric lesions | 2b | B | + |
| ➤ DCIS | | | |
| ≥ 5 cm or 2,5 cm + high grade (see DCIS) | 3b | B | +/- |
| if mastectomy is required | 3b | C | + |
| ➤ Male breast cancer | 2b | B | + |
| ➤ In the elderly | 3b | B | + |
| ➤ Add. FNA/CNB of LN (clinical/sonogr. suspicious) in order to enable SNE | 2b | C | + |

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Sentinel Lymph Node Excision (SNE): Indications II

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| | | | |
|---|----|---|------|
| ➤ During pregnancy and / or breast feeding (No blue duiy) | 3 | C | + |
| ➤ After previous tumor excision | 2b | B | + |
| ➤ Previous major breast surgery (e.g. reduction mammoplasty, mastectomy) | 3b | C | +/- |
| ➤ Ipsilateral breast recurrence after prior BCS and prior SNE | 4 | D | +/-* |
| ➤ SN in the mammarian internal chain | 2b | B | - |
| ➤ After axillary surgery | 3b | B | +/-* |
| ➤ Prophylactic bilateral / contralateral mastectomy | 3b | B | - - |
| ➤ Inflammatory breast cancer | 3b | C | +/- |

* Lymph node scintigraphy is necessary

Procedure after Neoadjuvant Therapy

Oxford / AGO
LoE / GR

- **Marking of tumor** **5 D ++**
- **Surgery** **2b C ++**
- **Microscopically clear margins** **5 D ++**
- **Tumor resection in the new margins** **3b C +**

Surgery and Irradiation after Neoadjuvant Therapy

Oxford / AGO
LoE / GR

Breast surgery:

After the nadir of the leucocyte count

4 C ++

(2 to 4 weeks after the last chemotherapy)

If irradiation after Mastectomy

is recommended

2b B ++

< 6 weeks after surgery

Indication based on the initial stage prior NT

(cN+, cT3/4a-d)

Surgery after Neoadjuvant Therapy

**Oxford / AGO
LoE / GR**

Breast conservation after clinical response possible:

- | | | | |
|---|-----------|----------|-------------|
| ➤ Multicentric lesion | 3 | C | +/-* |
| ➤ cT4a-c | 2b | B | +/-* |
| ➤ Inflammatory breast cancer (in case of pCR) | 2b | C | +/-* |

Mastectomy is recommended:

- | | | | |
|--|-----------|----------|------------|
| ➤ If after re-excision no clear margins are achieved | 2b | C | ++ |
| ➤ Extensive DCIS | 5 | D | ++ |
| ➤ If irradiation is not feasible | 5 | D | +/- |

*** Study participation recommended**

Adjuvant Therapy after Primary Surgery

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| | Oxford / AGO LoE / GR | | |
|--|--------------------------|----------|------------|
| ➤ Start adjuvant systemic therapy and RT as soon as possible (a.s.a.p.) after surgery | 1b | A | ++ |
| ➤ Start of adjuvant chemotherapy after surgery a.s.a.p., and prior to RT | 1b | A | ++ |
| Without cytotoxic therapy: | | | |
| ➤ Start irradiation 6-8 weeks after surgery | 2b | B | ++ |
| ➤ Start endocrine therapy after surgery and a.s.a.p. | 5 | D | ++ |
| ➤ Tamoxifen concurrent with radiotherapy | 3b | C | + |
| ➤ AI concurrent with radiotherapy | 2a | B | +/- |

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Breast Cancer Surgery Oncologic Aspects (2/15)

Further information and refernces: Kühn T., Kümmel S.

Update Januar 2014

Screened data bases: Pubmed 1998 - 2014, ASCO 2013, SABCS 2013, ESMO 2013

Screened consensus conference:

- Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members.
Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013.
Ann Oncol. 2013 Sep;24(9):2206-23. doi: 10.1093/annonc/mdt303. Epub 2013 Aug 4.

Cochrane library:

- <http://onlinelibrary.wiley.com/cochranelibrary/search>

Pretherapeutic Assessment (3/15)

Further information:

Preoperative breast diagnosis is required for planing breast surgery and avoiding surgery in benign conditions. Breast palpation, actual mammography and breast ultrasound are mandatory. Breast imaging diagnostic is avoidable in LABC (e.g. bleedings, ulceration). Malignancy and tumor size can best be evaluated by using both imaging procedures. Suspicious microcalcifications can be further characterized by magnification views. MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer, however there is a need to reduce FP MRI detection. Randomized trials are needed to determine the clinical value of detecting additional disease which changes surgical treatment in women with apparently localized breast cancer. MRI could be an option in patients with ambiguous mammografic and/or ultrasound findings to further characterize the lesions and in young women at high risk of breast cancer. Histological examination of every suspicious breast lesion should be carried out preoperatively by (image-directed) percutaneous needle biopsy to warrant one-session definitive surgery. The relationship between benign and malignant lesions should not exceed 1:2 after open biopsy. FDG PET is not recommended for axillary staging of patients with newly diagnosed breast cancer because of it fails to detect axillae with small and few nodal metastases.

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Statement: Palpation

GCP

Statement: All Methods:

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Perioperative Staging (4/15)

Further information:

A history and physical examination are good clinical practice and an obligation in every patient. Chest X-ray, liver ultrasound and bone scan have been used for initial staging of breast cancer. Patients with early, low risk breast cancer do not benefit from routine staging procedures. The routinely examination of serum liver enzymes, chest X-ray , liver ultrasound and bone scans in patients with high risk disease (clinically N1 and/or G3, cT3) could be helpful to avoid an overtreatment in cases with distant metases. FDG-PET / PET-CT are valuable tools for detecting breast cancer recurrence and occult metastases, however a survival benefit due to early detection has not been proven yet. Moreover the technique is expensive and not everywhere available.

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Statement: history and physical examination
GCP

Statement: high metastatic potential / symptoms

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Evidence of Surgical Procedure (5/15)

Further information:

The standard surgical procedure for early breast cancer is breast conservation followed by radiation therapy. Ipsilateral breast tumor relapse rates should be lower than 10% after 10 years of follow-up. Randomised trials and clinical series of breast conservation report conflicting evidence relating to tumour size as a risk factor for local recurrence, although most studies report no association. There is little evidence to justify the use of tumour size alone as an exclusion criterion for breast-conservation therapy. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy. The skin sparing mastectomy with or without conservation of the nipple-areola complex and autologous reconstruction is a oncological safe treatment option in selected patients. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy according to Rotter-Halstedt.

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Statement: Nipple sparing mastectomy

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Breast Conservation (6/15)

Further information:

Excisional biopsy should be wire guided if the lesion is not palpable and specimen radiography should be performed. Radioguided occult lesion localisation' (ROLL) is a possible alternative to the commonly used 'wire-guided localisation' (WGL) of non-palpable breast lesions. Intratumoural injection of a radiotracer identifies both the primary tumour and the sentinel lymph nodes for intraoperative gamma probe guided dissection. The intraoperative radiography or ultrasound is in all cases of non-palpable lesions indicated (GCP). In breast conserving surgery the margins of the specimen have to be tumor free. There is no universal agreement on the width of the tumor free margin. Re-excision is required for a close margin < 1 mm in paraffin section. The re-excision is recommended in a period of < 4 weeks. Patients with involved margins, large tumour size and/or a DCIS component are more likely to have residual disease on re-excision. . The rate of re-excision even in experienced and large breast centers is about 20% (up to 25% in case of DCIS).

References:

Statement: Wire guided ...

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Breast Conservation Surgery (7/15)

Further information:

There are no randomized trials concerning BCS vs mastectomy in patients with multicentric breast cancer or inflammatory breast cancer. Multicentricity is defined as at least two separate lesions with a distance of > 4 cm. All indications for mastectomy in these patients are driven from the fact that local recurrence rate is significantly elevated in these patient groups. If there are no free margins after repeated excisions the option of mastectomy should be discussed with the patient.

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Axillary Lymph Node Dissection I (8/15)

Further information:

Axillary lymph node dissection improves clinical outcome only in patients with lymph node metastases. Axillary dissection is mainly a diagnostic procedure. Removal of tumor-free lymph nodes increases morbidity and has no prognostic impact. Available evidence suggests that quality assured sentinel lymph node biopsy (SLNB) is a reliable predictor of axillary lymph node status with high levels of sensitivity (90-95%), specificity (100%), negative predictive value (95%) and accuracy (97%).

In case of adequate multimodal treatment axillary dissection is not associated with improved overall survival

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Statement: Axillary lymph node dissection

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Statement AMAROS trial

Axillary dissection and radiotherapy are both associated with excellent regional control rates in clinically node-negative patients with a positive sentinel lymph node as has been shown in the AMAROS trial. Patients who received radiotherapy had significant less arm morbidity compared to patients who underwent axillary dissection. However some questions remain regarding this study such as the necessity of internal and supra-infra node irradiation. Due to many open questions the publication of the full paper of the AMAROS trial should be awaited before radiotherapy is used routinely to replace axillary surgery in patients, who require axillary dissection

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Surgical Treatment of Axillary Lymph Nodes Pre and Post Nact (9/15)

Further information:

Statement surgical intervention in the axilla before or after Neoadjuvant Chemotherapy

Axillary surgery is a diagnostic procedure with the primary goal to provide prognostic information for the planning of treatment decisions. In the adjuvant setting the axillary status may tailor systemic (in luminal B) and regional treatment. The systemic treatment in patients, who undergo neoadjuvant therapy is (in general) predefined. In these patients the histopathologic response to chemotherapy (that includes response in the breast and the lymph nodes) is an important prognostic factor with a high potential to tailor future systemic and regional treatment decisions. Therefore it would be more reasonable to perform SLNB after NACT in order to provide this important prognostic factor.

SLNB after neoadjuvant chemotherapy is, however, associated with less favourable success rates (detection rate, false negative rate) compared to SLNB in primary surgery (as shown in the SENTINA trial). This relates especially to patients, who present initially with positive lymph nodes and convert to a negative axillary status under NACT. For patients with initially negative lymph nodes the success rates for SLNB after NACT appear more favourable although evidence from sufficiently powered prospective trials is lacking. Furthermore no data regarding oncologic endpoints (disease free survival, overall survival) are yet available for the SLN procedure after NACT.

In conclusion SLNB prior to NACT is a safe procedure, that can spare many patients with advanced tumors from axillary dissection. SLNB after NACT is an important future perspective, that should, however, be performed within clinical trials to provide the urgently awaited data on clinical outcome.

No references

Sentinel Lymph Node Excision: Indications I (10/15)

Further information:

Sentinel lymph node excision (SLN) has become a standard surgical procedure in patients with clinically and sonographically negative axilla (cN0).

Sonographically criteria for the definition of „negative lymph node“ has to be precised. Indication for SNE is not only focused on small tumours but nowadays possible and proven in many indications (cT3, Multicentricity). In large DCIS or if a mastectomy is required - SNE should be offered to the patient. Although male breast cancer patients presented with older age and larger tumors than female breast cancer patients - SLN procedure in clinically node-negative men is feasible and accurate.

Preoperative ultrasound guided needle biopsy is accurate for initial staging of the axilla and should be used for women with invasive breast cancer and clinical suspect axillary lymph nodes, as has been shown in a recently published metaanalysis

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Breast Cancer Res Treat. 2012 Oct;135(3):781-9. doi: 10.1007/s10549-012-2231-1. Epub 2012 Sep 1

Sentinel Lymph Node Excision: Indications I (11/15)

Further information:

There are only few experiences reported about SNE during pregnancy. The radioactive dosage of the applied radiocolloid is estimated very low and therefore not harmful for the unborn. Nothing is known about altered lymph drainage during pregnancy. The Bundesamt für Strahlenschutz has stated in a letter to the author that no fetal harm will be expected after application of 11 MB at the day of surgery and that therefore is no indication for termination of pregnancy. By performing a SLN biopsy, a large proportion of patients with PABC may be spared the risk of a complete axillary lymph node dissection. Therefore the commission decided a + for the procedure during pregnancy. The management of internal mammary nodes (IMNs) in breast cancer is still controversial. RCT are in progress. Data from small series have shown that second SLNB after previous SLNB is technically feasible and likely effective in selected breast cancer patients. A SLNE is not recommended in patients with prior surgery and large disturbing the lymphatic vessels in the breast or axillar or between these regions. In Inflammatory BC the feasibility of SNE is of limited data. Suspected clinical lymph node involvement should be clarified with FNA/CNB to avoid overtreatment in case of axillary lymph node dissection with negative involvement after clinically suspicious lymph nodes.

For patients, who undergo repeat SLNB after previous axillary surgery lymphoscintigraphy should be performed because a high rate of extraaxillary SLN has been described in this setting.

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Statement: pregnancy

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Statement: all others

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Singletary SE. Surgical management of inflammatory breast cancer. *Semin Oncol.* 2008 Feb;35(1):72-7

Procedure after Neoadjuvant Therapy (12/15)

Further information:

Precise documentation of tumor location before – e.g. with intratumoral clip implantation -, during and at the end of primary systemic therapy (PST) is necessary. Surgery is an integral part of primary breast cancer treatment following PST. The aim of surgery is to completely remove invasive and non invasive breast cancer residues after PST and to obtain clear margins of at least 1 mm at pathology examination. No compromise should be made in surgical margins to obtain better cosmetic results. Under these circumstances excision within new tumor margins might be feasible according to current data.

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Surgery and Irradiation after Neoadjuvant Therapy (13/15)

Further information:

It is unknown whether preoperative radiotherapy following primary systemic therapy (PST) achieved similar results as radiotherapy following PST and surgery. Preoperative radiotherapy might result in higher rates of breast conservation without compromising cosmetic result.¹ However, preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with PST² and do not replace adequate surgery³⁻⁶ which should be performed after leucocyte nadir around 2 to 4 weeks following last cycle of chemotherapy.⁷ Adjuvant radiotherapy after PST should be administered according to the same recommendations made for those patients who do not receive PST.⁸⁻¹⁰ Even in patients with pathological complete response following PST whole breast irradiation is indicated after breast-conserving surgery.^{3,4} According to retrospective analyses the addition of radiation to PST and mastectomy reduces local regional recurrence and increases breast cancer specific survival for patients presenting with clinical T3 tumors or stage III and IV (ipsilateral supraclavicular nodal) disease and for patients with \geq four positive axillary nodes regardless of their response to PST.¹¹

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Surgery after Neoadjuvant Therapy (14/15)

Further information:

Primary systemic therapy (PST) to achieve breast conserving surgery is not indicated in multicentric cancer, if extensive DCIS is present or if radiotherapy is not feasible.¹⁻³

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Adjuvant Therapy after Primary Surgery (15/15)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Oncoplastic and Reconstructive Surgery

Oncoplastic and Reconstructive Surgery

- **Versions 2002–2013:**
**Audretsch / Blohmer / Brunnert / Dall /
Fersis / Hanf / Kümmel / Nitz / Rezai /
Rody / Scharl / Thomssen**

- **Version 2014:**
Lux / Rezai

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Definition of Oncoplastic Surgery

Oncoplastic surgery in its original form began as combining lumpectomy or quadrantectomy with local or regional tissue rearrangement so that the breast should be conserved and reshaped so as to avoid significant deformity.

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Range of Options for Breast Reconstruction

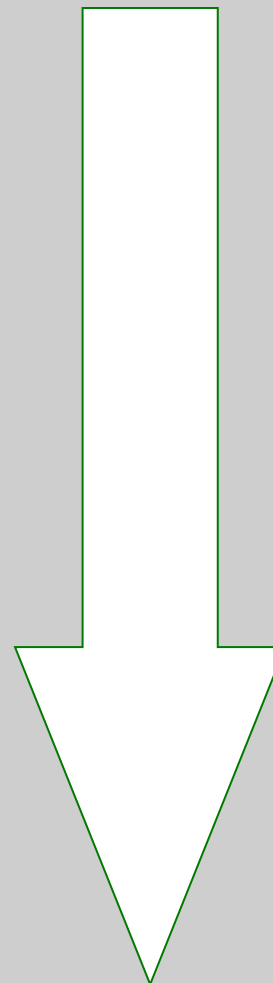
Implant

Latissimus

TRAM

Microsurgery

- DIEP
- SIEA
- SGAP



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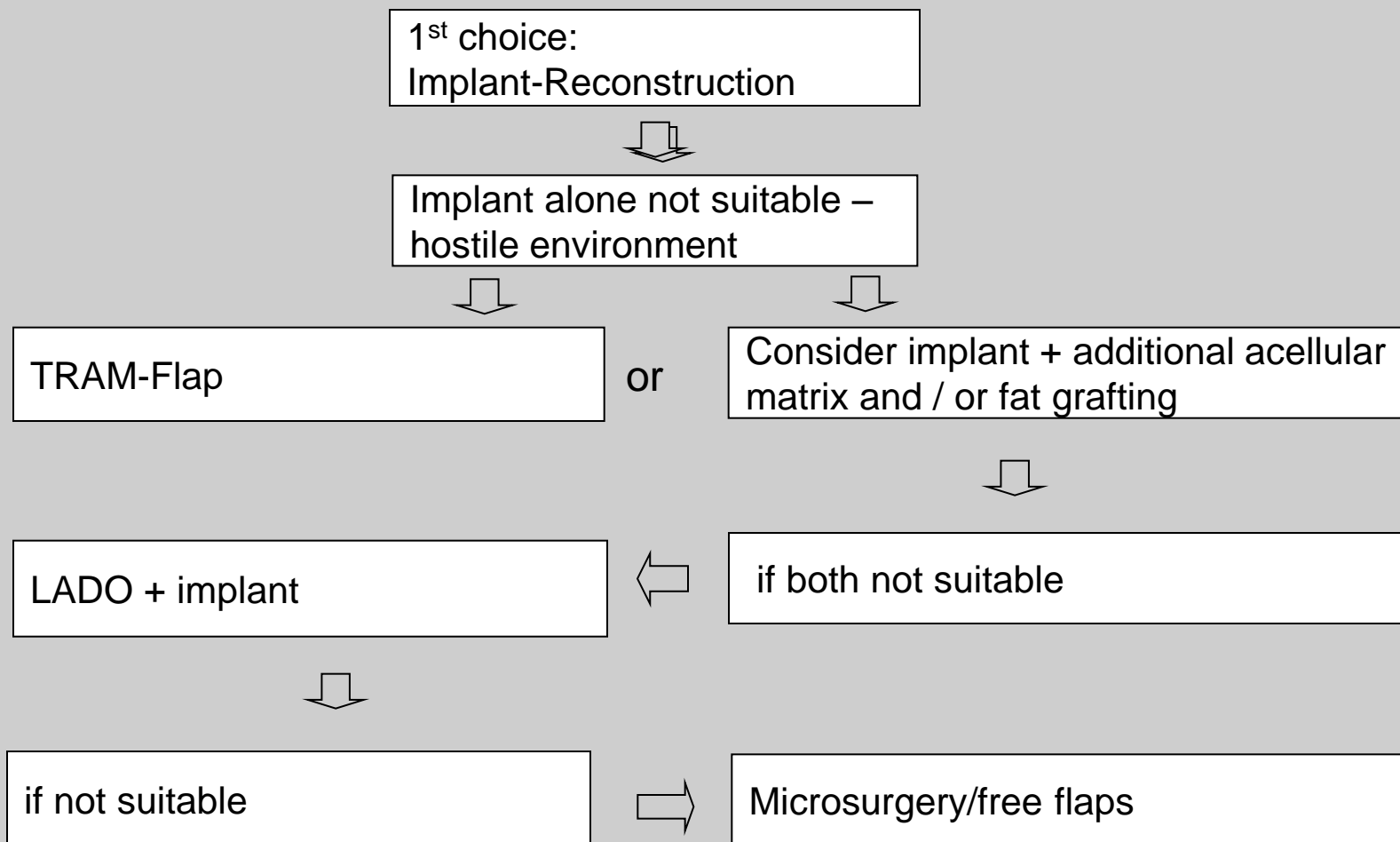
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Sumner A. Slavin, M.D

Algorithm of Breast Reconstruction

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Postmastectomy Implant Reconstruction

Oxford / AGO LoE / GR

- **Use of silicone filled breast implants
(no systemic health hazards
documented, no influence on OS
and detection of recurrence)**

2a B +

- **Implant reconstruction (IR)**

2a B +

- **IR without radiotherapy (RT)**

2a B ++

- **IR following MX and RT**

2b B +/-

- **IR prior to RT / following PBRT**

2a B +/-

- **No increase of complications by use of
acellular dermal matrix (ADM)**

3a C +/-

- **IR following Mx for local relapse after BCT**

2a B +/-

- **Periop. antibiotic therapy (at least 48 h)**

3b C +

Radiotherapy after Implant Breast Reconstruction I

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| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|--|---|---|-------------------------------|--------------------------|
| McCarthy CM PRS 2008 | Pre-or postop. radiation no significant risk factors | Independent risk factors: smoking, obesity, hypertension, age >65 39% total complication rate | 2003-2004 prospective | 1170 Exp/impl rec. |
| Berry T Ann Surg Oncol 2010 | 70,1% sucessfull | Major complic.rate 24,4% +RT 45,4% | - | Total 1037 |
| Gross E/Cowen D Cancer Radiother 2010 Breast Cancer Res Treat 2010 | 41,4 % pts. satisfied | Risk factors for failure: <u>surgeon</u> , tumor size T3 or T4, smoking, pN+, Baker 3+4 32,5 % | 37 mths. 1998-2006 | 141 |
| Whitfield GA Radiother Oncol 2009 | 70 % free of CC after 6 years | CC p < 0.001 (30 % vs. 0 %) | 51 mths. | 41/110 |
| Christante D Arch Surg 2010 | not reported | 7 % vs. 44 % p<0.001 | 2000-2008 | 302 |
| Cordeiro PG PRS 2004 | n.s. acceptable | p=0,025 CC (68% vs. 40%) | 1995-2001 | 81/606 |
| McCarthy PRS 2005 | 80% satisfied no Baker IV | 40% no difference 50% 1 Baker grade up 10% 2 Baker grades up | FU 23,5 mths. 1998-2002 | |
| Cordeiro PG PRS 2006 | 95% pts. satisfied | 49,3% no CC | 1992-2004 prospective | 71/410 |
| Behranwala JPRAS 2006 | 60% free of CC after 4 years | CC p<0.001 (38,6% vs. 14,1%) | 2-5 years | 44/92br |
| Benediktson K JPRAS 2006 | Reop. n=16 free of CC after 5 years | CC p=0.01 (41,7% vs. 14,5%) | 2-5 years | 24/83 |

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Radiotherapy

after Implant Breast Reconstruction II

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| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|-----------------------------------|---|--|---------------------------|---|
| Tran Tet al. 2011 | no significant differences between irradiated and non-irradiated patients | more frequently lymphedema in radiated patients | 2005-2010 retrospective | 175 (25.7% with radiotherapy), 54,8% implant based reconstruction |
| Brooks S et al. 2012 | 70,1% successfull expander/implant reconstruction | 28,4% (<50y.), 37% (>50y.) 27,5 (BMI<30), 49% (BMI>30) | 2000-2006 retrospective | 560 |
| Nava MB, Plast Reconstr Surg 2011 | not reported | Implant + RT 6.4% Expander + RT 40% | - | 257 exp vs. implant rec |
| Aristei C et al. 2012 | outcome excellent/good 57/84 | pain n=7 lympedema n=6 cutaneous toxicity n=5 subcutaneous toxicity n=19 Capsular contracture: IA 14/89 IB 47/89 II 10/89 III 11/89 IV 8/89 | 1997-2009 FU 50 months | 101 |

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Radiotherapy after Implant Breast Reconstruction with use of ADM

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| Reference | Year | Level of Evidence/ Animal Model | RT and ADM Reconstructions (n) | Findings |
|---------------------------------------|------|------------------------------------|-----------------------------------|--|
| Literature review | | | | |
| Bindingnavele et al. ²⁵ | 2007 | III | TE/I (5) | Irradiated ADM versus nonirradiated cohort demonstrated a 20% vs. 10.7% overall complication rate and 20% versus 0 expander loss rate at 10-mo follow-up |
| Breuing and Colwell ³⁰ | 2007 | III | TE/I (10) | One (10%) irradiated expander was lost compared with none in the nonirradiated cohort; 85% expander fill volume at initial surgery |
| Spear et al. ³¹ | 2008 | III | TE/I or A (11) | Radiation leads to 11-fold increase in complication rate of HADM patients with PMRT; highly select patients with prior BCT ($n = 4$) developed no complications |
| Nahabedian ³² | 2009 | III | TE/I (23) | Higher incidence of infection (8.7% vs. 3.9%), incisional dehiscence (13% vs. 1.3%), and seroma (13% vs. 2.6%) in HADM irradiated versus nonirradiated breasts |
| Seruya et al. ³³ | 2010 | III | TE/I or A (54) | HADM reconstruction patients receiving PMRT developed a 29.6% capsular contracture rate compared with 0.7% in nonirradiated HADM patients at an overall follow-up of 16.1 mo |
| Nguyen et al. ³⁴ | 2010 | III | TE/I (28) | For irradiated breasts, HADM use led to a significantly higher explantation rate compared with total muscle coverage (10.7% vs. 0, $p = 0.02$) |
| Israeli and Feingold ³⁵ | 2011 | III | TE/I (17) | Within HADM reconstructions, irradiated breasts had a significantly higher overall complication rate (50% vs. 3.5%, $p = 0.0005$) and expander loss rate (17.6% vs. 2.9%, $p = 0.04$) than nonirradiated breasts |
| Rawlani et al. ³⁶ | 2011 | III | TE/I (26) | HADM patients receiving PMRT compared with no radiation had nonsignificantly higher overall complication, infection, flap necrosis, and implant exposure rates |
| Salzberg et al. ³⁷ | 2011 | III | I (21) | Irradiated breasts had a fourfold higher rate of complications for HADM breast reconstructions (14.3% vs. 3.9%) |
| Colwell et al. ³⁸ | 2011 | III | I (51) | Higher overall complication rate (25.2% vs. 13.9%, $p = 0.005$); prior BCT/RT had a significantly higher complication rate (24.2%) over PMRT (16.7%) |
| Animal studies | | | | |
| Dubin et al. ²⁶ | 2000 | 36 rat hind limbs | | No difference in HADM thickness or neovascularization when irradiated; low early fibroblast counts increasing to high late counts compared with non-irradiated controls |
| Ibrahim et al. ²⁷ | 2000 | 36 rat hind limbs | | No difference in HADM thickness when irradiated; diminished early recellularization and neovascularization increasing to normal levels by wk 12 |
| Komorowska-Timek et al. ²⁸ | 2009 | 41 rat implant capsules | | Irradiated HADM has diminished cellular invasion; however, HADM appears to decrease radiation-related inflammation and delays or diminishes pseudoepithelium formation |

Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review. *Plast Reconstr Surg.* 2012; 130(5 Suppl 2):27S-34S.

Muscle Fixation for Immediate Reconstruction after Mastectomy

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- **Autologous tissue (e.g. LDF*)**
- **Acellular dermal matrix (ADM)**
 - **No significant increase of long-term complication rate compared to implant without ADM**
 - **Less capsular contracture compared to two-stage expander/implant without ADM**
- **Synthetic mesh**

**Oxford / AGO
LoE / GR**

3b C +[#]

2b B +[#]

2b C

2b C

2b B +[#]

* LDF = Latissimus dorsi flap

Participation in register studies recommended

Summery of Outcomes of Studies Comparing ADM and Non-ADM BR

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| Author, y | Infection Rate* | | | TE Explantation | | | Seroma | | | Skin Necrosis [†] | | |
|-------------------------------------|-----------------|-------------|----------------------------|-----------------|-------------|--------------------------|-----------|-------------|---------------------------|----------------------------|-------------|--------------------------|
| | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P | ADM (%) | Non-ADM (%) | P |
| Preminger et al, 2008 ¹⁴ | 1 (2.2) | 1 (2.2) | 0.999 | — | — | — | 3 (6.7) | 2 (4.4) | 0.645 | — | — | — |
| Sbitany et al, 2009 ¹⁵ | 4 (8) | 3 (6) | 0.99 | 4 (8) | 3 (6) | 0.99 | 3 (6) | 3 (6) | 1.0 | — | — | — |
| Nahabedian, 2009 ¹² | 22 (5.85) | 5 (5) | — | 20 (5.32) | 2 (2) | — | — | — | — | — | — | — |
| Lanier et al, 2010 ¹⁰ | 15 (28.9) | 9 (12.0) | 0.022[‡] | 10 (19.2) | 4 (5.3) | 0.02[‡] | 8 (15.4) | 5 (6.7) | 0.14 | 8 (15.4) | 4 (5.3) | 0.069 |
| Chun et al, 2010 ⁹ | 22 (8.2) | 1 (0.68) | 0.0016^{‡*} | — | — | — | 38 (14.1) | 4 (2.7) | 0.0003[‡] | 55 (20.5) | 6 (4.1) | 0.001[‡] |
| Nguyen et al, 2010 ¹³ | 11 (2.8) | 7 (3.4) | 0.291 | 6 (8) | 4 (1.6) | 0.013[‡] | — | — | — | — | — | — |
| Liu et al, 2011 ¹¹ | 13 (4.8) | 5 (2.4) | 0.172 | — | — | — | 19 (7.1) | 8 (3.9) | 0.136 | 31 (11.6) | 17 (8.3) | 0.282 |
| Present Study | 5 (16.1) | 2 (4.5) | 0.118 | 5 (16.1) | 2 (4.5) | 0.118 | 6 (19.4) | 6 (13.6) | 0.537 | 2 (6.5) | 1 (2.3) | 0.566 |

— represents not reported.
Values in bold indicate statistical significance.
*Rate of major infection, when differentiated, defined by admission for IV antibiotics or explant.
[†]Skin necrosis requiring debridement.

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Hanna KR, DeGeorge BR Jr, Mericli AF, et al. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013; 70(1): 10-5.

Summary of Characteristics and Conclusions of Studies Comparing ADM and Non-ADM Breast Reconstruction

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| Author, y | No. Patients | | No. Breasts | | Conclusions |
|-------------------------------------|--------------|---------|-------------|---------|--|
| | ADM | Non-ADM | ADM | Non-ADM | |
| Preminger et al, 2008 ¹⁴ | 45 | 45 | — | — | <ul style="list-style-type: none"> • No increased morbidity with ADM use • ADM use does not facilitate increased rate of expansion |
| Sbitany et al, 2009 ¹⁵ | 50 | 50 | 92 | 84 | <ul style="list-style-type: none"> • No increased morbidity with ADM use • Faster reconstruction time with ADM use |
| Nahabedian, 2009 ¹² | 76 | 285 | 100 | 376 | <ul style="list-style-type: none"> • No increased risk of infection with ADM use • Incisional dehiscence, seroma, and infection incidence ↑ with XRT |
| Lanier et al, 2010 ¹⁰ | 52 | 75 | — | — | <ul style="list-style-type: none"> • ↑ rate of infection with ADM use in larger breasts |
| Chun et al, 2010 ⁹ | — | — | 269 | 146 | <ul style="list-style-type: none"> • ↑ rate of infection, seroma and skin necrosis with ADM use • ↑ rate of infection may be related to ↑ rate of skin necrosis and seroma |
| Nguyen et al, 2010 ¹³ | 41 | 163 | 75 | 246 | <ul style="list-style-type: none"> • ↑ rate of explantation in ADM group, possibly due to learning curve |
| Liu et al, 2011 ¹¹ | 192 | 151 | 266 | 204 | <ul style="list-style-type: none"> • ↑ overall rate of complications with ADM, increased BMI, smoking, and increased initial volume and larger implant |
| Present study | 31 | 44 | 38 | 62 | <ul style="list-style-type: none"> • No significantly increased morbidity with ADM use • Equivalent satisfaction between ADM and submuscular patients |

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Hanna KR, DeGeorge BR Jr, Mericli AF, et al. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013; 70(1): 10-5.

Lipofilling

Oxford / AGO
LoE / GR

➤ **Lipofilling after implant-based reconstruction**

2a B +

➤ **Lipofilling after breast-conserving therapy**

4 D +/-

➤ **Autologous adiposederived stem cells (ASCs)-enriched fat grafts**

5 D -

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Follow-up Results after Lipofilling

| | Patients (n) | Follow-up before lipofilling (months) | Local recurrence before n (%) | Follow-up after lipofilling, months (minimum– maximum) | Local recurrence after n (%) | Local recurrence after (incidence per 100 person- years) | Distant metastases (n) | Interval from lipofilling to recurrence (months) | Interval from lipofilling to metastasis (months) | Patients with free- disease survival at 5 years from surgery (%) | Patients with free-disease survival at 8 years (%) |
|-------------------------|-----------------|--|--|---|---------------------------------------|---|------------------------------|---|---|--|---|
| Rigotti et al. [20] | 137 | 23 | 4 (2.92) | 60 | 5 (3.6) | 0.72 | 9 | 20 ± 12 | 21 | 95.6 | 91.5 |
| Riefjens et al. [21] | 155 | 35.2 | – | 18.3 (6–49) | 1 (0.6) | 0.43 | 0 | 2 weeks | – | – | – |
| Petit et al. [23] | 321 | 26 | – | 26 (1–128) | 13 (4.0) | 1.87 | 13 | – | – | – | – |
| Petit et al. [22] | 513 | 39.7 | 0 (0) | 19.2 (1–107) | – (2.4) | 1.5 | 15 | – | – | – | – |
| Riggio | 60 | 56.5 | 1 (1.66) | 92.2(5–132) | 2 (3.3) | 0.43 | 4 | 47 ± 14.8 (minimum 21– maximum 73) | 28.5 | 93.3 | 90 |

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Riggio E, Bordoni D, Nava MB. Oncologic surveillance of breast cancer patients after lipofilling. Aesthetic Plast Surg. 2013; 37(4): 728-35.

Further
Information

References

Postmastectomy Pedicled Flap Reconstruction

**Oxford / AGO
LoE / GR**

Reconstruction (BR) with autologous tissue

- TRAM, latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)
- Delayed TRAM in risk patients
- Ipsilateral pedicled TRAM
- Radiotherapy:
 - BR following RT
 - BR prior to RT
(dependent on quality of blood supply)

3b C +

3a B +

3b A +

4 C +

3b C +/-

Free Tissue Transfer

Oxford / AGO
LoE / GR

Free tissue transfer

- Free TRAM-flap
- DIEP-flap
- SIEA-flap
- SGAP- / IGAP-flap
- Free gracilis flap (TMG)
- Latissimus dorsi free flap

3b B +/-

4 C +/-

4 C +/-

Advantage:

- Free TRAM and DIEP are potentially muscle-sparing procedures

Disadvantages:

- Time- and personnel-consuming microsurgical procedure
- Intensified postoperative monitoring
- Higher rate of re-operations
- Higher total failure rate
- Pre-reconstruction RT increases rate of vascular complications
- No higher patient satisfaction than with pedicled TRAM in multivariate analysis

Pedicle vs. Free Tissue Transfer

Oxford / AGO
LoE / GR

- **Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used**
- **Autologous abdominal-based reconstructions have the highest satisfaction in all patient groups without any difference**
- **Perforator flaps appear to have a higher risk for fat necrosis than free or pedicle TRAM**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration in all flap techniques**

3a A ++

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Flap-Implant Combination

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Flap-implant combination

TRAM, LDF* + implant

- IR following RT
- IR prior to RT

4 C +

3b C +

5 D -

Advantages:

- TRAM: staged procedure preferable
- Improved implant coverage
- Suitable for radiated tissue

Disadvantage:

- Muscle contraction (LDF)

* LDF = Latissimus dorsi flap

Timing of Breast Reconstruction

Oxford / AGO
LoE / GR

➤ Delayed BR

3b B ++

- No interference with adjuvant procedures (CHT, RT)
- Disadvantage: loss of skin envelope

➤ Immediate BR

3b B ++

- Preferential in combination with partial Mx (BCT)
- Mandatory: SSM / NSM
- Avoidance of a postmastectomy syndrome

➤ „Delayed-immediate“ BR

3b B +/-

Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|-----------|
| ➤ Skin sparing mastectomy (SSM/NSM) | | | |
| ➤ Safe (same recurrence rate as MX) | 2b | B | ++ |
| ➤ Higher QoL for patients | 2b | B | ++ |
| ➤ NAC can be preserved under special conditions | 2b | B | ++ |
| ➤ Feasible after mastopexy / reduction mammoplasty | 4 | C | ++ |
| ➤ Skin incisions ⇒ different options possible: | | | |
| ➤ Periareolar („purse-string“) (higher risk of necrosis) | | | |
| ➤ Reduction pattern: „inverted-T“ or vertical | | | |
| ➤ Inferior lateral approach, inframammary fold | | | |
| ➤ Lowest incidence of complications | 2b | B | + |

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SSM / Nipple SM

| Author | Cases reported | Partial skin necrosis | Local recurrence | Time period |
|---|-----------------------|---|------------------------------------|--------------------------|
| Lanitis S et al. 2010 Ann Surg | 1104 SSM 2635 NSSM | -- | 6,2% SSM 4,2% NSSM n.s. | 1997–2009 Metaanalyse |
| Jensen JA Ann Surg Oncol 2010 | 99 | 6 % | 2,7 % | Median FU 60,2 mths |
| Yi M, Kronowitz SJ 2010 Cancer | 799 SSM 1011 CM | - | n.s. (local+syst. 6.6%) | 2000-2005 |
| KIM HJ Ann Surg 2010 | 368 SSM 152 NSSM | 9.6% NAC | 0.8% SSM 2.0% NSSM (1.3%NAC) | 07.2001-12.2006 |
| Paepke S Ann Surg 2009 | 109 SSM (96 NSM) | 1,0 % of nipple necrosis | no rec. in the nipple | 2003-2006 |
| Chen CM 2009 PRS | 115 (62 benign) | Loss of NAC: 5.2% Occ.ca. 3.5% Necrosis | -- | 1998-2008 |
| Garwood ER 2009 Ann Surg | 170 | Cohort 1: 16% Cohort 2: 11% | 0,6% | 2001-2007 |
| Yano K et al. 2007 Breast Cancer | 128 | 3,1% | 2,3% | 2001–2005 |
| Petit JY et al. 2006 Breast Cancer Res Treat | 106 NSM | 4,7% Loss of NAC | 0,9% Far from NAC | 2002–2003 |
| Gerber B et al. 2003 Ann Surg | 112 (Incl.61 NSM) | 0% | 5,4% | 1994–2000 |

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Bilateral Risk Reducing Mastectomy in Healthy Women (RRBM)

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- **RRBM reduces breast cancer incidence**
- **RRBM in deleterious BRCA1/2 mutation**
- **RRBM in high risk (i.e. lifetime risk $\geq 30\%$ or heterozygote risk $\geq 20\%$) but index case negative for BRCA1/2 mutations**
- **High risk and no BRCA counselling in specialized centre***
- **Non-directive counselling prior to RRBM**
- **RRBM should be considered with other prophylactic surgical options incl. salpingoophorectomy (BSO)**
- **Further need for education of physicians regarding possibilities and advantages of RRBM**

**Oxford / AGO
LoE / GR**

| | | |
|-----------|----------|-------------|
| 1b | A | ++ |
| 2a | B | ++* |
| 3a | C | +/-* |
| 5 | D | -- |
| 2b | B | ++* |
| 2a | A | ++* |
| 1b | A | ++ |

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*Counselling, risk prediction and follow-up in specialised centres recommended

Types of Risk Reducing Mastectomy in Healthy Women (RRBM)

Oxford / AGO
LoE / GR

**Risk Reducing Mastectomy
reduces breast cancer incidence;
bc-spec mortality reduction likely**

| | | | |
|---------------------------------|----|---|-----|
| ➤ Simple mastectomy | 2b | B | + |
| ➤ RRBM by SSM | 2b | C | + |
| ➤ RRBM by NSM (NAC sparing) | 2b | C | + |
| ➤ Contralateral prophylactic MX | 4 | C | +/- |

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| Author | Cases reported | Complete loss of flap | Lipo-necrosis | Hernias in donor region |
|--|---|-----------------------|---------------|--|
| Gill PS et al 2004 PRS | 758 | 0,5% | 15,4% | 0,7% |
| Guerra et al 2004 Ann Plast Surg | 280 | 0% | 12,5% | 2,1% |
| Nahabedian et al 2005 PRS | 110 | 2,7% | 6,4% | 2,7% |
| Blondeel PN 1999 PRS | 100 | 2% | 13% | 1% |
| De Greef C et al 2005 Ann Chir Plast Esthet | 100 | 4% | 7% | 2% |
| Garvey PB et al 2006 PRS | 96 | 0% | 17,7% | 1% 9,4% bulges |
| Xu H 2009 PRS | 113 | 3,5 % | 17,7% | 0 % hernia 0,9 % bulges (med. FU only 12,3 months!) |
| Wan DC 2010 PRS | 275 1) fTRAM 2) MS fTRAM 3) DIEP | | | 1+2)BMI<30: 0 % 1)BMI>30: 0 % 2)BMI>30: 2,8 % 3)BMI<30: 6,1 % 4)BMI>30:14,3% |

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| Author | Cases reported | Complete loss of flap | Liponecrosis partial flap loss | Hernias/ Bulges in donor region |
|--|----------------------------------|-------------------------------|--|---------------------------------|
| Munhoz AM et al 2007 Breast J (on DIEP and SSM) | 30 | 3,7% | 7,4% | 3,7% |
| Lindsey JT. 2007 PRS | 140 | 6,4% | -- | -- |
| Hofer SO et al. 2007 Ann Plast Surg | 175 | 0,6% | 8,6% | -- |
| Peeters WJ 2009 PRS | 202 | n.a. | 49% Clinical 14% US 35% | n.a. |
| Selber JC 2010 PRS | fTRAM 569 DIEP 97 | 0,2% 1,0% n.s. | 4,1% 2,1% n.s. | 1,9% 0 n.s. |

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| Author | Cases reported | Complete loss of flap | Liponecrosis partial flap loss | Hernias/ Bulges in donor region |
|--|-------------------|-----------------------|--------------------------------|---------------------------------|
| Garvey BP et al. PRS 2011 | 228 | n.a. | 8,3/3,3% | n.a. |
| Conroy K et al. PRAS 2011 | 3 | - | - | 3 epigastric hernia |
| Momoh AO et al. Ann PS 2011 | 217 | n.a. | n.a. | 2,3%/0% |
| Andree C. et al. Med Sci Monit 2012 | 1068 | 0,8% | n.a. | n.a. |
| Gart, M et al. J Am Coll Surg 2013 | 609 Free Flaps | 5,7% | n.a. | n.a. |

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| Author | Reported cases | Complete loss of flap | Liponecrosis | Hernias in donor region |
|--|----------------|-----------------------|--------------|-------------------------|
| Watterson PA, Bostwick J. 1995 PRS | 556 | 0 | 10,6% | 8,8% |
| Kroll SS (f-TRAM) 2000 PRS | 279 | 0,4%(1,1%) | 15,1% | |
| Lacotte B, Lejour M 1994 Ann Chir Plast Esthet | 156 | 0 | 10% | 0 |
| Clugston PA, Maxwell GP 2000 PRS | 252 | 0 | 9,1% | 5,8% |
| Petit JY, Rietjens M 1997 Ann Chir Plast Esthet | 310 | 0 | 10,2% | 7% |
| Rezai M IGCS 2010 | 234 | 0 | 10,2% | 0,6% |
| Brunnert 2001 unpublished | 776 | 0 | 8,4% | 0,4% |
| Kim EK 2009 Ann Plast Surg | 500 | major fl. 0,2 % | 14,2% | 3% (bulges) |
| Chun YS 2010 PRS | 105 biped, | 0 | 11,4% | 2,9% |

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Pediced / Free TRAM II

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| Author | Reported cases | Complete loss of flap | Liponecrosis | Hernias in donor region |
|------------------------------------|----------------|-----------------------|------------------|-------------------------|
| Momoh AO et al. Ann PS 2011 | 197 | n.a. | n.a. | 2,3%/0% |
| Garvey BP et al. PRS 2011 | 228 | n.a. | 11,3/2,8% | n.a. |

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| Author | Patient satisfaction | Failure complications | Observation period | Pts. RT/CTR |
|--------------------------------------|---|---|--------------------|----------------------|
| Williams JK 1997 PRS | unchanged | nature of complications changes from fat necrosis to fibrosis | 1981–1994 | 19/680 |
| Soong IS 2004 Clin Oncol (Radiol) | cosmesis 85% good to excellent | no difference | 1995–2001 | 25/-- |
| Mehta VK 2004 Breast | no problems | 10% skin desquam. 30% grade 2 erythema | 1995–2000 | 22/-- |
| Huang CJ 2006 PRS | | fat fibrosis 8% n.s. | 1997–2001 | 82/109 |
| Kronowitz SJ 2009 PRS | Radiation Therapy and BR: A critical review of the literature | | >1985 | 49 articles reviewed |

Radiotherapy after Autologous Reconstruction II

| Author | Patient satisfaction | Failure Complications | Observation period | Pts. RT/CTR |
|--|----------------------|--|--------------------|------------------------------------|
| Barry M, Breast Cancer Res Treat. 2011 Metaanalysis | not reported | OR = 0.21; 95% CI, 0.1-0.4 [autologous vs. implant-based] | - | 1105 Implant vs. Autologous Recon. |

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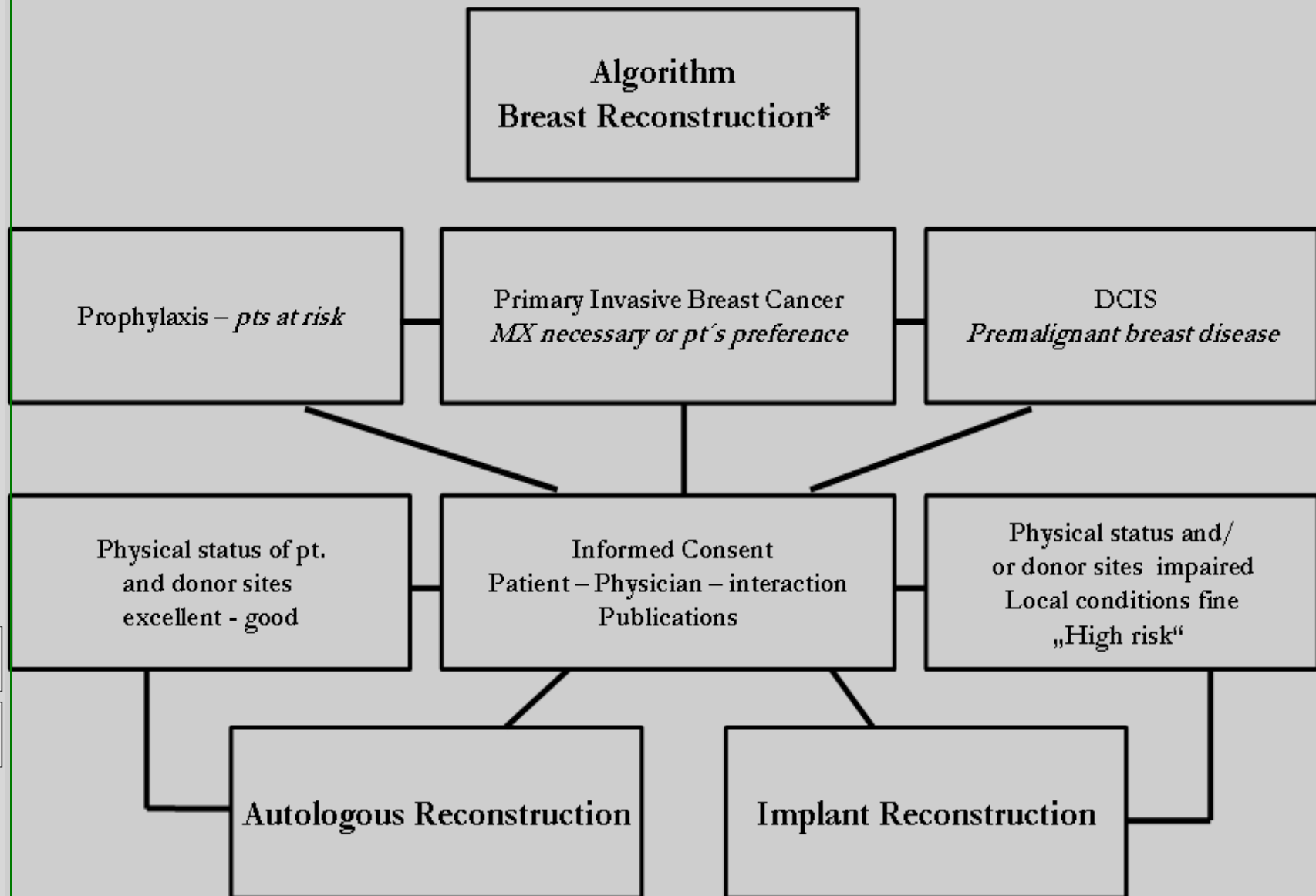
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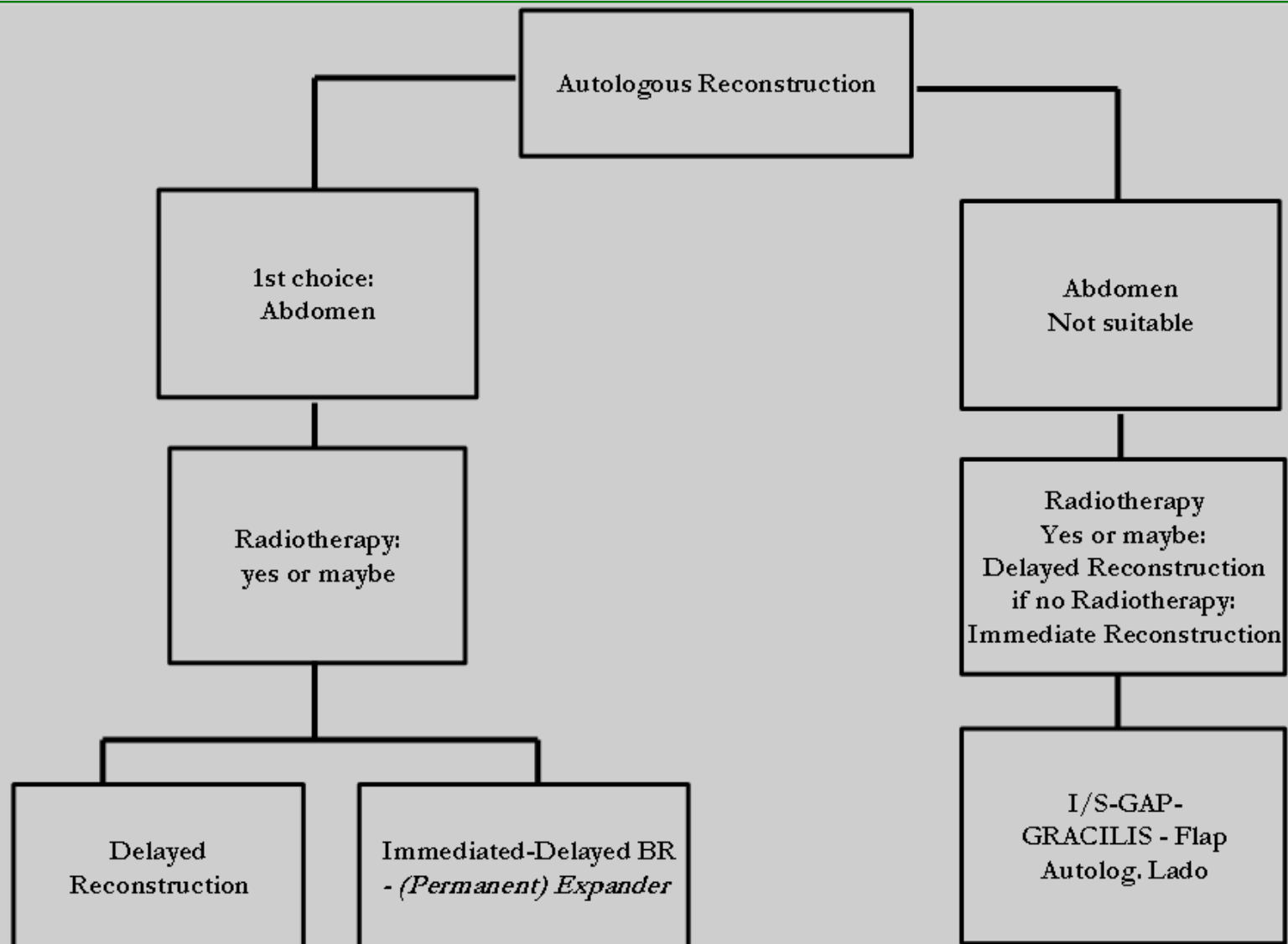
References

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*Brunnert, K. Gyn. Prax., Band 31, 2007

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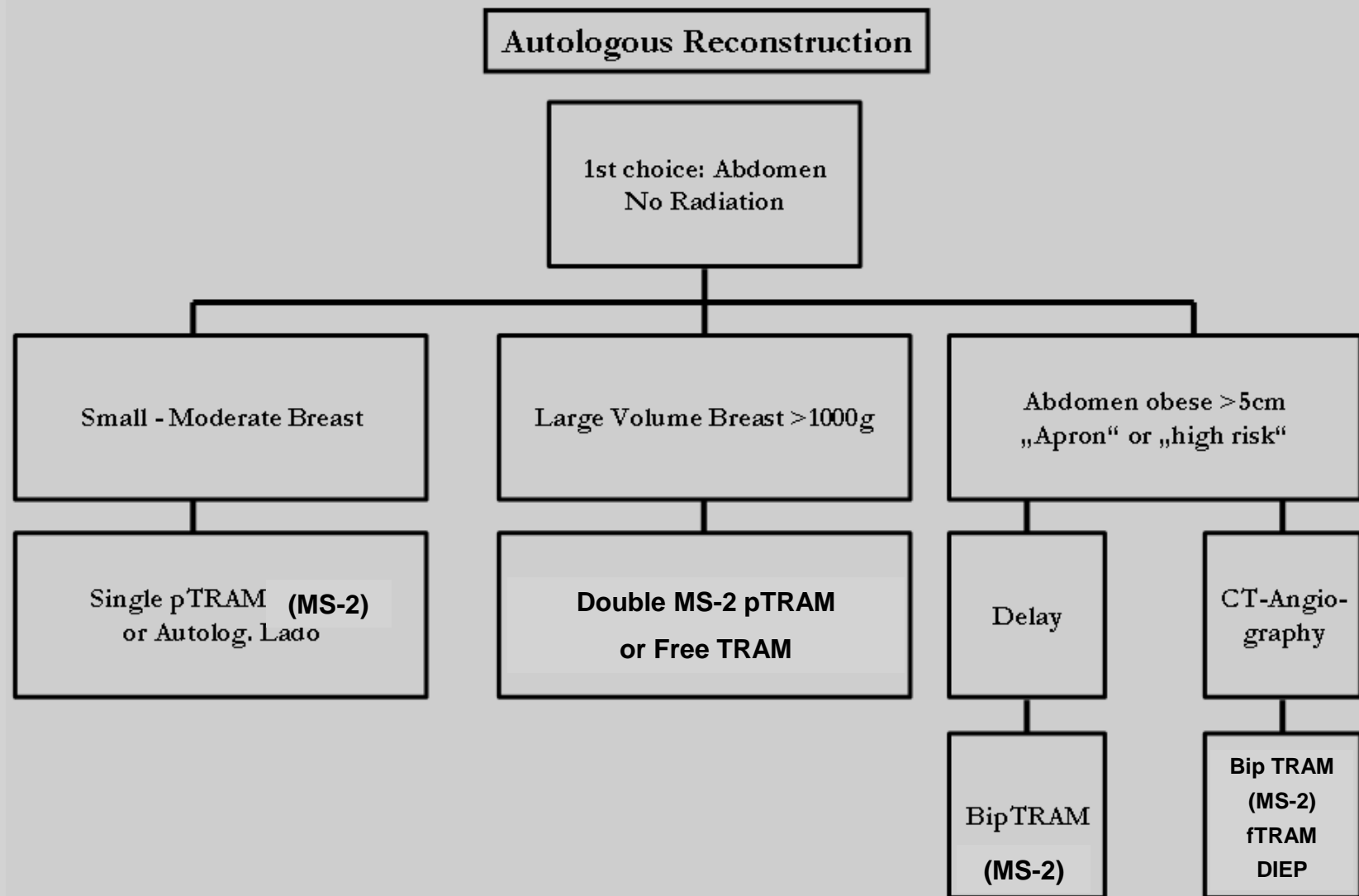
References

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Algorithm of Autologous Breast Reconstruction (2)

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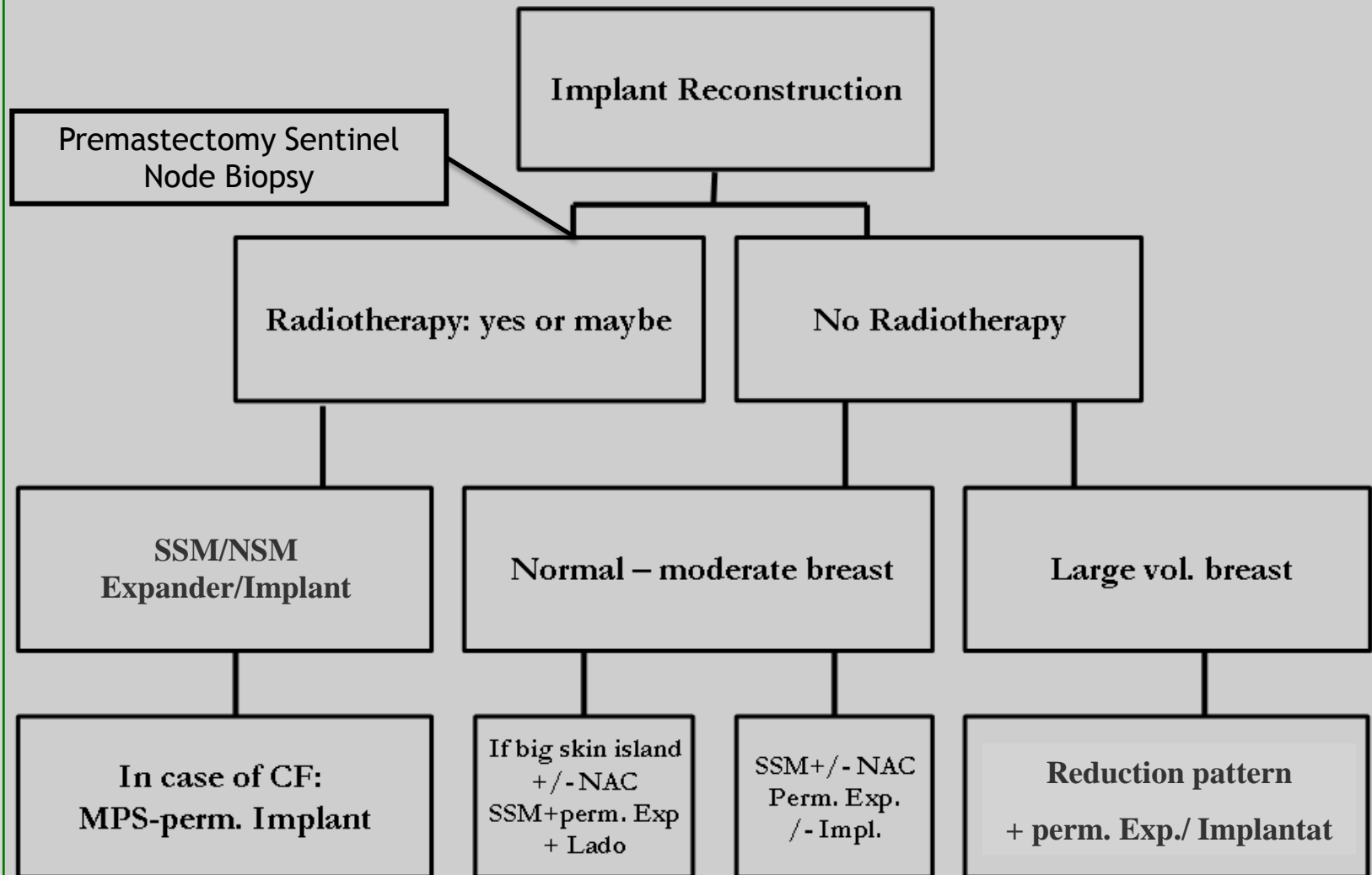


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Oncoplastic and Reconstructive Surgery (2/34)

Further information:

Verwendete Literatur-Datenbanken:

Pubmed 2003 - 2013

Cochrane data base (z.B. Cochrane Breast Cancer Specialised Register)

Suchbegriffe: breast reconstruction; ... AND random allocation, ... AND cohort study

Einteilung in EBM-Grade nach Jeremy Howick, Iain Chalmers, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. "The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document)". Oxford Centre for Evidence-Based Medicine.

<http://www.cebm.net/index.aspx?o=5653>

und Thomssen et al. SOPs für die Überarbeitung der AGO-Leitlinien zum Mammakarzinom 2006 2

Verwendete Guidelines zu Diagnostik und Therapie des Mammakarzinoms:

National Institute of Health (NIH): <http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/>

American Association of Clinical Oncology (ASCO) and Technology Assessments:

<http://www.asco.org/portal/site/ASCO/menuitem>. (Practice Guidelines),

Canadian Medical Association (CMA): <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

NCCN 2007: <http://www.medscape.com/files/editorial/articles/548868/breast.pdf>

Aesthetics must play a key role in the surgery of the breast in order to avoid deformities which could have a negative impact on a patient`s self esteem irrespective of age. With the help of oncoplastic surgery free margins due to wide

excisions of malignant tumors are possible without compromising the shape of the breast thus preserving physical integrity. As a result oncoplastic surgery plays an integral role in the primary surgical treatment of BC.

Definition of oncoplastic surgery (3/34)

No further information

References:

Scott Spear, Washington DC, 2009

Range of Options for Breast Reconstruction (4/34)

No further information

References:

Sumner A. Slavin, MD

Algorithm of Breast Reconstruction (5/34)

No further information

No references

Postmastectomy Implant Reconstruction (6/34)

Further information and references:

Link to no documented systemic health hazards and to IR following RT and prior RT and to advantage of implant reconstruction:

Silicone breast implants are safe and important building blocks in the variety of reconstructive techniques in breast reconstruction. The two-year results of the Michigan Breast Reconstruction Outcomes Study shows, that in regard to general satisfaction there is no statistical difference concerning implant or autogenous reconstruction. Only from an esthetic viewpoint seems the breast reconstruction with living tissue superior. But the increasing use of Post-mastectomy-radiation-therapy (PMRT) endangers the aesthetic results of immediate (IBR) or delayed breast reconstruction with implants. On the other hand the survey of recent publications on immediate implant reconstruction demonstrates the feasibility of implant reconstruction, despite the fact, that certain complications as capsular contracture (CC) are more frequent after PMRT and IBR. On the other hand in the majority of cases CC is curable by a single operative procedure. Implant reconstruction in previously radiated patients proves to have a higher rate of perioperative complications after performing expander/implant breast reconstruction, but the absolute rate of complications remained low in the analysis of a prospectively maintained database of 1522 reconstructions in 1221 patients by Peter G. Cordeiro of the Memorial Sloan-Kettering Cancer Center. This is the reason for keeping expander/implant reconstruction after prior radiotherapy in their reconstructive armamentarium.

If the necessity of postsurgical radiotherapy is not known at the time of mastectomy and reconstruction there is the possibility of a delayed-immediate reconstruction. After SSM a traditional or permanent expander is implanted till the final decision about RT is made; after completion of RT or if not necessary at all immediately the planned standard reconstruction is performed.

In case of unilateral implant reconstruction alone a development of asymmetry over time has to be considered. The most predictable results in implant reconstruction can be achieved with the bilateral use of implants or the combination with a latissimus dorsi flap. Implants are generally placed in a dual plane position, i.e. a partial muscular coverage of the implant.

Only if there is a wide supple muscular pocket (lato+pectoralis m.) is a complete coverage advisable (tension-induced pain otherwise possible).

One hundred and seventy-eight immediate breast reconstructions performed at the Cambridge Breast Unit between 1.1.2001 and 31.12.2005 were identified. RT was delivered using a standard UK scheme of 40 Gray in 15 fractions over 3 weeks. The influence of hormones and chemotherapy as well as postoperative RT on time to development of severe CC after implant-based reconstruction was explored in univariate and multivariate analysis. One hundred and ten patients had implant-based reconstructions with a median follow-up of 51 months. In the RT group (41 patients), there were 8 patients with severe CC requiring revisional surgery, a crude rate of 19.5%, with actuarial rates of 0%, 5%, 5%, 21%, 30% and 30% at 1, 2, 3, 4, 5 and 6 years follow-up. In the unirradiated group, there were no cases of severe CC. This difference is highly significant ($p < 0.001$). Hormones and chemotherapy were not significantly associated with severe CC (Whitfield et al.).

One hundred and thirty-six breast reconstructions were studied in 114 patients: 62 reconstructions were performed using submuscular implants alone and 74 had an implant-assisted latissimus dorsi myocutaneous flap using a McGhan 150 biodimensional permanent expander implant. Data were prospectively collected on capsule contracture, geometric measurements, photographic assessments and pain scores. The median follow-up was 4 (range, 2-5) years. The mean age of the 114 patients studied was 45 (range, 20-77) years. Forty-four reconstructed breasts received RT. Capsule formation was detected in 13/92 (14.1%) reconstructed breasts with no RT and in 17/44 (38.6%) reconstructed breasts with RT. On univariate analysis, RT was the only variable related to capsule formation ($p < 0.001$). Significant differences in geometric measurements of symmetry were identified in patients with capsules compared with those without capsules. Photographic assessments were worse in the capsule group: mean photo score 8 (95% CI 8, 8.5) compared with the no capsule group 6.5 (95% CI 5, 7.5), $p < 0.001$. Persistent pain two years or more after surgery was present in 8/30 patients with capsules and 1/106 with no capsule group, $p < 0.01$. Capsule formation is three times more likely to occur after IBR in association with an RT field. However, as more than 60% of patients do not get capsules despite RT at four years, implant-assisted tissue expansion techniques using a biodimensional device is a viable breast reconstructive option in selected cases (Behranwala et al.).

Further data is based on a publication from 2012. Regarding that radiotherapy of reconstructed breasts is associated with major complications and poor cosmetic outcome Aristei et al. assessed complication rates, the link between risk factors

and prosthesis removal, as well as cosmetic outcomes [Aristei et al., 2012]. From 1997 to 2009, 101 consecutive patients received RT after breast reconstruction because of risk factors for relapse (92) or because relapse had occurred (9). At RT, 90 patients had temporary tissue expanders and 11 had permanent implants. Twelve patients underwent neo-adjuvant chemotherapy; all patients received adjuvant chemo- and/or hormone therapy. At a median follow-up of 50 months, late toxicities occurred in 28 patients: pain in 7, lymphedema in 6, G1 cutaneous toxicity in 5, and subcutaneous toxicity in 19 (2G1, 9G2, 7G3, 1G4), with more than one side effect in 12. In 8 patients the prosthesis ruptured (3), was displaced (3), was displaced and ruptured (1), or lost shape (1). Capsular contracture was classified in 89 patients as IA in 14, IB in 47, II in 10, III in 11, and IV in 7. Twelve prostheses (11.9%) were removed. The only significant factor for prosthesis removal was age ($p = 0.007$). Judgments of cosmetic results were available from 81 physicians and 84 patients. Outcome was excellent/good in 58/81 physician judgments and in 57/84 patient evaluations. Overall inter-rater agreement on outcome was good (κ -value 0.64; 95% CI: 0.48-0.79). The authors conclude that RT to reconstructed breasts was associated with low rates of late toxicity and prosthesis removal. Cosmetic outcomes were, on the whole, good to excellent.

References:

Alderman AK et al. Does patient satisfaction with breast reconstruction change over time? Two-year results of the Michigan Breast Reconstruction Outcomes Study. J Am Coll Surg 2007 Jan;204(1):7-12

Cordeiro PG, McCarthy CM. A single surgeon's 12-year experience with tissue expander/implant reconstruction: part I. A prospective analysis of early complications. Part II. An analysis of long-term complications, aesthetic outcomes, and patients satisfaction. Plast Reconstr Surg 2006 Sep 15; 118(4): 825-839.

Kronowitz SJ et al. Delayed-immediate breast reconstruction. Plast Reconstr Surg. 2004;113(6):1617-28.
Radiother Oncol. 2008 Oct 31. [Epub ahead of print] Links

Whitfield GA, Horan G, Irwin MS, Malata CM, Wishart GC, Wilson CB. Incidence of severe capsular contracture following implant-based immediate breast reconstruction with or without postoperative chest wall radiotherapy using 40 Gray in 15 fractions. *J Plast Reconstr Aesthet Surg*. 2006;59(10):1043-51. Epub 2006 Jun 12. [Links](#)

Behranwala KA, Dua RS, Ross GM, Ward A, A'hern R, Gui GP. The influence of radiotherapy on capsule formation and aesthetic outcome after immediate breast reconstruction using biodimensional anatomical expander implants.

Aristei C, Falcinelli L, Bini V, Palumbo I, Farneti A, Petitto RP, Gori S, Perrucci E. Expander/implant breast reconstruction before radiotherapy: outcomes in a single-institute cohort. *Strahlenther Onkol*. 2012 Dec;188(12):1074-9. doi: 10.1007/s00066-012-0231-z. Epub 2012 Nov 1.

Link to no influence on DFS and detection of recurrence:

A matched retrospective cohort study was performed. Only patients with invasive breast cancer who had 2 years or more of follow-up and/or patients who had recurrence within 2 years of their primary cancer were included. In total, 618 patients who underwent mastectomy for invasive breast cancer from 1995 until 1999 were evaluated. Three hundred nine patients who had immediate, tissue expander/implant reconstruction were matched to 309 women who underwent mastectomy alone on the basis of age (± 5 years) and breast cancer stage (I, II, or III). The incidence of locoregional recurrence following mastectomy was 6.8 percent in patients who had reconstruction and 8.1 percent in patients who had mastectomy alone (log rank $p = 0.6015$). Median time to detection of a locoregional recurrence was 2.3 years (range, 0.1 to 7.2 years) in the reconstructed cohort and 1.9 years (range, 0.1 to 8.8 years) in the nonreconstructed cohort ($p = 0.733$). Permanent implants were removed following infection in one patient and patient request in two. These results suggest that there is no difference in the incidence of locoregional recurrence in breast cancer patients who undergo immediate, tissue expander/implant reconstruction compared with those patients who do not have reconstruction. Prosthetic breast reconstruction does not appear to hinder detection of locoregional cancer recurrence. In the majority of patients, management of locoregional recurrence does not necessitate removal of a permanent prosthesis.

Reference:

Plast Reconstr Surg. 2008 Feb;121(2):381-8. Links

Breast cancer recurrence following prosthetic, postmastectomy reconstruction: incidence, detection, and treatment.

McCarthy CM, Pusic AL, Sclafani L, Buchanan C, Fey JV, Disa JJ, Mehrara BJ, Cordeiro PG.

Link to independent of age:

Between 1999 and 2004, 63 elderly patients underwent an immediate reconstruction after breast cancer treatment at the European Institute of Oncology. A conservative treatment, combined with breast repair by plastic surgical techniques, was performed in 14 patients. In the remaining 49 patients, a modified radical mastectomy was necessary in 30 breasts, a total mastectomy in 19, a subcutaneous mastectomy in one case and a radical mastectomy in one patient. Three nipple-sparing mastectomies, along with intra-operative radiotherapy, were performed in two patients. A definitive silicone implant was used in 41 breasts and a skin expander in eight cases. A latissimus dorsi flap was performed in two patients, a pedicled transverse rectus abdominis muscle (TRAM) flap in two cases and a local advancement fasciocutaneous flap in another two patients. In all patients, surgery was well tolerated despite patient age. No systemic and medically unfavourable events occurred in the immediate and late postoperative period. Infection occurred in four patients (6.34%) and partial necrosis of the mastectomy flaps in three cases (5.5% of the mastectomies). Capsular contracture grade III and IV was reported in four cases (8.89%). Total implant removal was rated 12.24%, due to infection (three prostheses), exposure (one expander) and capsular contracture grade IV (two implants). Implant-based technique of breast reconstruction should be made available to the elderly population.

References:

J Plast Reconstr Aesthet Surg. 2008 Dec 23. [Epub ahead of print] Immediate breast reconstruction in the elderly: can it be considered an integral step of breast cancer treatment? The experience of the European Institute of Oncology, Milan. De Lorenzi F, Rietjens M, Soresina M, Rossetto F, Bosco R, Vento AR, Monti S, Petit JY.

Link to dual mesh-muscle pocket:

In this series of 77 reconstructed breasts, the overall complication rate was 26%, with surgical revision in 12% and reconstructive failure with implant removal in 8% of patients. The performance of an abdominal lift did not significantly influence the complication rate. The dual mesh-muscle technique rendered the use of bigger implants possible, with a significant difference between the resected weight (302 \pm 140g) and the implant size (346 \pm 93g) ($P < 0.05$). This indicates that lower-pole restriction can be overcome and the original volume can be reconstituted or even augmented. In conclusion, the dual mesh-muscle technique is comparatively reliable and permits to overcome the limitations with definitive implant-based IBR after SSM without increasing the risk for postoperative complications even if abdominal skin is recruited to compensate for the skin removed with the mastectomy.

References:

Wettstein R, Elias B, Bächle A, Vlastos G, Harder Y. Dual mesh-muscle pocket with/without abdominal lift for immediate implant-based breast reconstruction after skin-sparing mastectomy. J Plast Reconstr Aesthet Surg. 2008 Dec 15. [Epub ahead of print]

Link to dual alloderm-muscle pocket:

A matched, retrospective cohort study was performed. Medical records of patients who underwent immediate TE/I reconstruction from 2004 to 2005 were reviewed. Two cohorts were identified: (1) underwent TE/I reconstruction with AlloDerm, and (2) underwent standard TE/I reconstruction. Individuals were matched 1:1 on the basis of: expander size (\pm 100 mL), history of irradiation, and indication for mastectomy. Cohorts were compared for intraoperative volume injected (mL), rate of postoperative expansion (mL/ injection), number of expansions, and time to completion of expansion (days). Incidence of complications was evaluated. Pairwise comparisons were performed using the Wilcoxon sign rank test and McNemar test. Ninety immediate TE/I reconstructions were evaluated. Forty-five TE/I-AlloDerm reconstructions were matched to standard TE/I reconstructions. Intraoperatively, expanders in the AlloDerm and non-AlloDerm cohorts were filled to a mean volume of 223.8 and 201.1 mL ($P = 0.180$). Median number of expansions performed was 5 and 6 in the

AlloDerm and non-AlloDerm cohorts ($P = 0.117$). There was no difference in the mean rate of postoperative tissue expansion (AlloDerm: 97 mL/injection versus non-AlloDerm: 95 mL/injection [$P = 0.907$]), nor in the incidence of complications ($P = 0.289$). Minor complications occurred in 13.1% of AlloDerm cases (cellulitis [$n = 3$], seroma [$n = 3$], hematoma [$n = 1$]). Although this study does not address AlloDerm's efficacy in decreasing morbidity or improving esthetic outcomes in TE/I reconstruction, it indicates that AlloDerm does not increase the rate of tissue expansion after immediate TE placement. It does not, however, appear to increase the risk of postoperative complications.

Reference:

Preminger BA, McCarthy CM, Hu QY, Mehrara BJ, Disa JJ. The influence of AlloDerm on expander dynamics and complications in the setting of immediate tissue expander/implant reconstruction: a matched-cohort study. *Ann Plast Surg*. 2008 May;60(5):510-3. [Links](#)

[Link to higher complication rate for immediate implant reconstruction:](#)

The authors reviewed all breast reconstructions after mastectomy for breast cancer performed under the supervision of a single surgeon over a 6-year period at a tertiary referral center. Reconstruction method and timing, patient characteristics, and complication rates were reviewed. Reconstruction was performed on 240 consecutive women (94 bilateral and 146 unilateral; 334 total reconstructions). Reconstruction timing was evenly split between immediate ($n = 167$) and delayed ($n = 167$). Autologous tissue ($n = 192$) was more common than tissue expander/implant reconstruction ($n = 142$), and the free deep inferior epigastric perforator was the most common free flap ($n = 124$). The authors found no difference in the complication incidence with autologous reconstruction, whether performed immediately or delayed. However, there was a significantly higher complication rate following immediate placement of a tissue expander when compared with delayed reconstruction ($p = 0.008$). Capsular contracture was a significantly more common late complication following immediate (40.4 percent) versus delayed (17.0 percent) reconstruction ($p < 0.001$; odds ratio, 5.2; 95 percent confidence interval, 2.3 to 11.6). Autologous reconstruction can be performed immediately or delayed, with optimal aesthetic outcome and low flap loss risk. However, the overall complication and capsular contracture incidence following immediate tissue

expander/implant reconstruction was much higher than when performed delayed. Thus, tissue expander placement at the time of mastectomy may not necessarily save the patient an extra operation and may compromise the final result.

Reference:

Sullivan SR, Fletcher DR, Isom CD, Isik FF. True incidence of all complications following immediate and delayed breast reconstruction. *Plast Reconstr Surg.* 2008 Jul;122(1):19-28. Links

Mirzabeigi MN, Lee M, Smartt JM Jr, Jandali S, Sonnad SS, Serletti JM. Extended trimethoprim/sulfamethoxazole prophylaxis for implant reconstruction in the previously irradiated chest wall. *Plast Reconstr Surg.* 2012 Jan;129(1):1e-7e.

Patients who have undergone prior chest wall irradiation can present as challenging candidates for implant reconstruction because of troublesome rates of infectious complications. The issue of antibiotic prophylaxis remains controversial, and evidence-based postoperative strategies to reduce implant infections have not been well described in the literature. The purpose of this study was to determine the efficacy of extended trimethoprim/sulfamethoxazole therapy in preventing implant infections in the irradiated chest wall. A retrospective chart review of hospital and office records was performed on all patients undergoing implant reconstruction performed by a single surgeon (J.M.S.) from August of 2005 to March of 2008. Before 2007, the senior author used 5 to 7 days of cephalosporin prophylaxis. Subsequent to this period, the prophylactic regimen was amended to provide patients with previous chest wall irradiation prophylactic trimethoprim/sulfamethoxazole for 30 days after implant insertion. Fifty-one implant reconstructions, in the setting of prior ipsilateral chest wall irradiation, were performed. The mean follow-up time was 39 months. The infection rate for the routine cephalosporin group was 35 percent as compared with 8 percent for the extended trimethoprim/sulfamethoxazole group ($p = 0.038$). After multivariate analysis, extended trimethoprim/sulfamethoxazole remained the only significant factor that influenced the rate of infection ($p = 0.05$). The mean time to infection was 13 weeks for the routine cephalosporin group and 1.5 weeks for the extended trimethoprim/sulfamethoxazole group ($p = 0.044$). Extended trimethoprim/sulfamethoxazole therapy demonstrates preliminary evidence as an effective adjunctive measure for reducing the rate of implant infections in breast reconstruction. Clinical question/level of evidence: therapeutic, III.

The use of acellular dermal matrix (ADM) for for implant-based breast reconstruction does not appear to increase or decrease the risk of complications, but it might provide psychological and aesthetic benefits [Clemens and Kronowitz, 2012]. The MEDLINE and EMBASE databases were reviewed for articles published between January of 2005 and February of 2012 on breast reconstruction using acellular dermal matrix in the setting of radiation therapy. The authors also reviewed their institutional experience of consecutive patients who met these criteria between January of 2008 and October of 2011. Thirteen articles were identified for review: three animal studies on acellular dermal matrix and 10 with level III evidence of its use in humans. The 10 clinical studies included 246 irradiated patients. The M. D. Anderson experience included 30 irradiated acellular dermal matrix patients for a total of 276 irradiated patients evaluated in this review. In general, the studies reviewed here suggest that although acellular dermal matrix increases the incidence of seroma formation and infection, it does not increase the overall complication rate. Use of acellular dermal matrix in implant-based breast reconstruction in the setting of radiation therapy did not predispose to higher infection or overall complication rates or prevent bioprosthetic mesh incorporation. However, the rate of mesh incorporation may be slowed. Its use allowed for increased intraoperative saline fill volumes, which improved aesthetic outcomes and allowed patients to awake from surgery with a formed breast. However, further multicenter or single-center randomized controlled trials that provide high-quality, level I evidence are warranted.

Reference:

Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review.

Radiotherapy after Implant Breast Reconstruction I (7/34)

Further information and references:

Bennett SP, Fitoussi AD, Berry MG, Couturaud B, Salmon RJ. Management of exposed, infected implant-based breast reconstruction and strategies for salvage. J Plast Reconstr Aesthet Surg. 2011 Oct;64(10):1270-7. Epub 2011 Jun 25.

Complications of implant-based breast reconstruction are rare but mastectomy flap necrosis and peri-implant infection are the most frequent and remain an important cause of early implant failure. This study aimed to compare the results of three different management strategies employed to deal with these complications at our institution. A consecutive series of 71 infected/exposed prostheses in 68 patients over a 20-year period were analysed. Management strategies included explantation and delayed reconstruction, implant salvage and explantation and immediate autologous reconstruction. Only 19 of 45 (42%), managed with implant removal, went on to delayed reconstruction. Methods of delayed reconstruction were distributed equally between implant-only, implant and autologous tissue and autologous-only reconstructions. The implant was successfully salvaged in nine cases, but reducing the implant size or introducing new tissue as a flap increased the success from 45% to 53%. Three patients with infected implant-only breast reconstruction underwent explantation and immediate conversion to autologous-only reconstructions. All the three interventions reviewed here have their place in the management of infected implant-based breast reconstructions. It is noteworthy that following implant removal, the likelihood of the patient proceeding to delayed reconstruction of any kind is similar to the likelihood of successful salvage (42% vs. 45%). This study population had high numbers of exposed implants in irradiated fields. Reducing implant size or introducing new tissue in the form of a flap increases the chances of successful implant salvage. In the presence of mild infection, removal of exposed/infected implants and immediate conversion to an autologous-only reconstruction can prove to be successful.

Radiotherapy after Implant Breast Reconstruction II (8/34)

Further information and references:

Tran T, Tran T, Miles D, Hill M, Lum SS. The impact of radiation on surgical outcomes of immediate breast reconstruction. *Am Surg*. 2011 Oct;77(10):1349-52.

We sought to determine the differences in surgical outcomes associated with adjuvant radiation versus no radiation in patients undergoing concurrent breast oncologic and reconstructive operations. A retrospective review of patients who underwent combined oncologic and plastic surgeries for breast diseases from January 2005 to June 2010 was compared for demographic factors and outcomes by receipt of radiation therapy. During the study period, 175 patients were identified; 25.7 per cent received radiation therapy. Mean patient age was 51 years and median follow-up was 355 days. Overall, 80.2 per cent of patients underwent mastectomy; 19.8 per cent partial mastectomy; 42.1 per cent autologous tissue reconstruction; and 54.8 per cent implant-based reconstruction. There were no significant differences between radiated and nonradiated patients in rates of overall or oncoplastic-specific complications. Lymphedema was the only complication seen more frequently in the radiated arm ($P = 0.03$). In our series of carefully selected patients undergoing a variety of reconstructive techniques for repair of partial or total mastectomy defects, radiation was not associated with worse outcomes in patients undergoing immediate breast reconstruction. With careful collaboration among plastic surgeons, breast surgeons, and radiation oncologists, patients requiring breast surgery may safely be considered for reconstruction of partial or total mastectomy defects when adjuvant radiation is required.

Brooks S, Djohan R, Tendulkar R, Nutter B, Lyons J, Dietz J. Risk factors for complications of radiation therapy on tissue expander breast reconstructions. *Breast J*. 2012 Jan;18(1):28-34. doi: 10.1111/j.1524-4741.2011.01182.x. Epub 2011 Nov 20.

Radiation therapy has been shown to increase complication rates of tissue expander/implant breast reconstructions. The purpose of this study was to evaluate patient characteristics to assess their impact on complications. A retrospective review

of patients who underwent mastectomy plus tissue expander/implant reconstruction from January 2000 to December 2006 was performed. The main outcome of interest was the development of postoperative complications. Analyses were performed to detect risk factors for complications. A total of 560 patients were included in the study. A total of 385 patients underwent unilateral and 174 underwent bilateral tissue expander/implant reconstructions, for a total of 733 reconstructions. A total complication rate of 31.8% and a major complication rate of 24.4% were calculated. The risk factors associated with a significantly increased incidence of complications were age greater than 50 years, body mass index (BMI) greater than 30, and radiation. Women younger than 50 years had a complication rate of 28.4%, whereas women older than 50 years had a complication rate of 37.0%. Women with a BMI less than 30 had a complication rate of 27.5%, whereas women with a BMI greater than 30 had a complication rate of 49%. The major complication rate in nonradiated and radiated patients was 21.2% and 45.4%, respectively. Despite higher complication rates, tissue expander/implant reconstructions were successful in 70.1% of radiated patients. Based on this study, the ideal radiated patient would have a BMI less than 30 and be younger than 50 years of age to maximize the likelihood of a successful tissue expander/implant reconstruction.

Bennett SP, Fitoussi AD, Berry MG, Couturaud B, Salmon RJ. Management of exposed, infected implant-based breast reconstruction and strategies for salvage. *J Plast Reconstr Aesthet Surg*. 2011 Oct;64(10):1270-7. Epub 2011 Jun 25.

Complications of implant-based breast reconstruction are rare but mastectomy flap necrosis and peri-implant infection are the most frequent and remain an important cause of early implant failure. This study aimed to compare the results of three different management strategies employed to deal with these complications at our institution. A consecutive series of 71 infected/exposed prostheses in 68 patients over a 20-year period were analysed. Management strategies included explantation and delayed reconstruction, implant salvage and explantation and immediate autologous reconstruction. Only 19 of 45 (42%), managed with implant removal, went on to delayed reconstruction. Methods of delayed reconstruction were distributed equally between implant-only, implant and autologous tissue and autologous-only reconstructions. The implant was successfully salvaged in nine cases, but reducing the implant size or introducing new tissue as a flap increased the success from 45% to 53%. Three patients with infected implant-only breast reconstruction underwent explantation and immediate conversion to autologous-only reconstructions. All the three interventions reviewed here have their place in the management of infected implant-based breast reconstructions. It is noteworthy that following implant removal, the

likelihood of the patient proceeding to delayed reconstruction of any kind is similar to the likelihood of successful salvage (42% vs. 45%). This study population had high numbers of exposed implants in irradiated fields. Reducing implant size or introducing new tissue in the form of a flap increases the chances of successful implant salvage. In the presence of mild infection, removal of exposed/infected implants and immediate conversion to an autologous-only reconstruction can prove to be successful.

Radiotherapy after Implant Breast Reconstruction with use of ADM (9/34)

No further information

Reference:

Clemens MW, Kronowitz SJ. Acellular dermal matrix in irradiated tissue expander/implant-based breast reconstruction: evidence-based review.

Muscle Fixation for Immediate Reconstruction after Mastectomy (10/34)

Further information:

According to a national survey, greater than 50% of American Society of Plastic surgeons who predominantly perform implant-based breast reconstruction use ADM [Gurunluoglu et al., 2011].

There has been limited reported experience with the use of Strattice (LifeCell Corp., Branchburg, NJ), a porcine-derived acellular dermal matrix, in implant-based breast reconstruction. Salzberg et al. have evaluated their experience with this matrix [Salzberg et al., 2013]. Patients who underwent immediate single-stage or two-stage implant-based breast reconstruction with the assistance of Strattice were included in this study. Patient charts were reviewed for indications for mastectomy, adjunctive radiotherapy use, implant or expander volume, length of follow-up period, and type and incidence of complications during the follow-up period. Biopsies of ADM were taken for histological analyses. A total of 105 reconstructions were performed in 54 patients: 77% were prophylactic and 23% were oncologic. All, but 4, reconstructions were single stage. Mean implant volume of single-stage reconstructions were 444.1 (range: 150-700 cc) and mean expander volume after completion of expansion was 400 (range: 350-450). Mean follow-up period was 41.3 months (range: 35.5-48.4 months). Total complication rate was 8.6%. Complications occurred in 9 breasts: implant loss or explantation (3.8%), infection (3.8%), skin breakdown or necrosis (2.9%), seroma (1.9%), implant exposure (1.0%), and delayed skin healing (1.0%). Histological analyses of implanted ADM revealed a viable matrix with fibroblast infiltration and revascularization.

The infection rate of 3.8% with Strattice is comparable to that reported in pooled analyses of human ADMs (5.3%-5.6%) and in pooled analyses of traditional submuscular reconstructions (4.7%). The absence of clinically significant capsular contracture is noteworthy and is in concordance with the low rate reported in other published series of Strattice (0%-4.5%) as well as human ADMs (0%-4.3%).

In conclusion, over a mean 3.5-year follow-up period, low complication rates and good outcomes were observed with the use of Strattice that are comparable to those reported with human acellular dermal matrices.

A further study was performed by Hanna and colleagues [Hanna et al., 2013]. The authors compared tissue expansion properties, complication rates, and patient satisfaction for both operative techniques at the same institution. A retrospective review was completed on 75 patients and 100 tissue expander/implant-based breast reconstructions at a single academic institution from 2007 to 2010. Of these cases, 31 patients were reconstructed with ADM and 44 with a submuscular coverage technique. The submuscular group had a higher rate of minor complications (29.5% vs. 19.4%), whereas the ADM group had a higher rate of major complications (22.6% vs. 9%); however, this difference did not reach statistical significance. Total complications including seroma, hematoma, infection, skin necrosis, and explantation did not significantly differ between groups ($n = 13$ for ADM vs. 17 for submuscular, $P = 0.814$). Consistent with prior reports, ADM-based reconstructions were associated with significantly increased intraoperative fill volumes and lower total number of sessions to achieve final volume. Submuscular reconstructions required a significantly higher tissue expander fill volume. Eight patients in the submuscular group required surgical revision of the breast and inframammary fold, compared with 4 in the ADM group; however, this difference was not significant. Patient satisfaction was equivalent between the 2 groups; however, it was higher in patients with bilateral reconstruction and lower among those who had received adjuvant radiation therapy. Satisfaction with nipple reconstruction was inversely proportional to time elapsed from the procedure to survey conduction. This is the first study to perform a head-to-head comparison on the basis of patient satisfaction, the results of which may be useful in preoperative planning and counseling.

Regarding the rate of capsular contracture with ADM a number of published studies addressed this subject [Basu and Jeffers, 2012]. There is animal model and human histopathologic evidence showing that acellular dermal matrices slow or thwart the likely pathogenesis of capsular contracture. However, further long-term studies are needed to see if indeed these observations continue over time. A review of clinical studies show that the majority of clinical evidence lies in the direct-to-implant and two-stage tissue expander arena in reconstructive breast implant surgery [Basu and Jeffers, 2012]. Only two articles specifically address capsular contracture rates of acellular dermal matrices in revisionary aesthetic breast surgery. Most of the evidence is in the form of case series and retrospective, noncomparative review, underpowered, and of limited follow-up. Only one prospective review was found, and only one true comparative study between an acellular dermal matrix and nonmatrix cohort were found [Vardanian et al., 2011]. The comparative study did show that matrix use was associated with less capsular contracture (odds ratio, 0.18; 95 percent confidence interval, 0.08 to 0.43), providing the highest level of evidence to date (Level III). In addition, although the level of evidence remains III or lower

and the studies are limited by duration of follow-up or by small sample size (low power), the authors did find that all the clinical studies revealed capsular contracture rates ranging between 0 percent and 4 percent. Also, of the 15 clinical articles, only four involved a dermal matrix other than AlloDerm. The rates of capsular contracture in these four articles are similar to AlloDerm rates. However, only one study compared two different acellular dermal matrix products. While the evidence

for capsular contracture is suggestive, especially in postmastectomy breast reconstruction, the level of evidence should improve through better controlled studies with higher power, longer follow-up, and attention to the use of acellular dermal matrix and capsular contracture rates in revisionary breast surgery.

There is no difference in post-operative pain with or without ADM. A multicenter, blinded, randomized controlled study was designed to evaluate the effectiveness of acellular dermal matrix in the setting of tissue expander/ implant reconstruction [McCarthy et al., 2012]. The primary objective of the study was to determine whether the use of matrix would decrease patient-reported postoperative pain.

The randomized controlled trial was conducted at two U.S. centers from 2008 to 2011. Immediately following mastectomy, all patients were randomized to one of two treatment arms: (1) acellular dermal matrix-assisted, tissue expander/implant reconstruction; and (2) submuscular tissue expander/implant placement. All patients were blinded to their treatment arm. There were no differences seen in immediate postoperative pain ($p = 0.19$) or pain during the expansion phase ($p = 0.65$) between treatment arms. There was similarly no difference in postoperative narcotic use ($p = 0.38$). The rate of postoperative expansion did not differ between groups ($p = 0.83$). The results suggest that the use of acellular dermal matrix in the setting of tissue expander/implant reconstruction neither reduces postoperative pain nor accelerates the rate of postoperative expansion.

Moreover, the use of acellular dermal matrix in the context of a one-stage technique seems to be cost-effective compared to the two-stage use of expander followed by implant [Johnson et al., 2013]. Johnson et al. performed a cost analysis (using UK 2011/12 NHS tariffs as a proxy for cost) comparing immediate breast reconstruction using the new one-stage technique of acellular dermal matrix (Strattice) with implant versus the standard alternative techniques of tissue expander (TE)/implant as a two-stage procedure and latissimus dorsi (LD) flap reconstruction. Clinical report data were collected for operative time, length of stay, outpatient procedures, and number of elective and emergency admissions in

our first consecutive 24 patients undergoing one-stage Strattice reconstruction. Total cost to the NHS based on tariff, assuming top-up payments to cover Strattice acquisition costs, was assessed and compared to the two historical control groups matched on key variables. Eleven patients having unilateral Strattice reconstruction were compared to 10 having TE/implant reconstruction and 10 having LD flap and implant reconstruction. Thirteen patients having bilateral Strattice reconstruction were compared to 12 having bilateral TE/implant reconstruction.

For unilateral cases, our results suggest that funding Strattice is less costly (£3685 versus £4985) than tissue expansion and delayed exchange for permanent implant, and considerably less costly than LD reconstruction (£3685 versus £6321). Patient benefit appears to be at least as good, and if it were shown to be greater in a health economic study, immediate reconstruction with Strattice would be described as “dominating” unilateral tissue expansion. For bilateral cases, the use of Strattice in the index operation (and in any subsequent unplanned surgery) is more expensive (£6771 versus £5478) than reconstruction with tissue expansion. This reflects an anomaly in the current reimbursement system in England, in which reimbursement of bilateral mastectomy is the same as unilateral mastectomy, although average hospital costs are selfevidently higher in bilateral than in unilateral mastectomy patients.

The cost analysis shows a financial advantage of using acellular dermal matrix (Strattice) in unilateral breast reconstruction versus alternative procedures.

Regarding the use of synthetic meshes several retrospective studies are available. These can be used in the following patients:

- Patients undergoing IBBR after SSM or NSM with well preserved skin soft tissue proportions,
- Patients with primary or secondary prophylactic subcutaneous mastectomy,
- Patients undergoing nipple areola complex sparing subcutaneous mastectomy and well preserved skin soft tissue proportions,
- Patients with tuberous breasts, Poland syndrome or other congenital deformities.

Dieterich et al. have performed a retrospective analysis of 42 patients undergoing immediate or delayed implant based breast reconstruction (IBBR) using a titanium-coated polypropylene mesh (TCPM) over a 26-month period [Dieterich et al., 2012]. The aim of this study was to discuss indications, limitations and complications of TCPM in IBBR. Primary endpoints were incidence of infection and expander/implant with mesh removal due to infected fluid collection or

extrusion. In two patients, mild hematoma, seroma or infection occurred. Skin necrosis or capsular contraction was observed in one patient. Mesh explantation was needed in 3 cases. These events were higher among the first cases and in patients with postoperative skin infection ($p = 0.003$). In conclusion, TCPM seems to be a helpful tool for implant stabilization in terms of lateral stabilization and fixation of the musculus pectoralis major in selected patients with adequate soft tissue cover. In comparison to ADM, TCPM is cheaper and initial results are promising. In patients with poor soft tissue cover ADM should be used.

Further follow-up data are necessary - the participation in register studies is recommended.

The scarless latissimus dorsi flap is an effective method for providing durable homogenous device coverage in the thinner patient (body mass index <24). With the advent of acellular dermal matrices, device coverage has been made simpler, but this comes at a cost. Coverage is thin, the matrix is not initially vascularized, and products are expensive. For these reasons, use of the scarless latissimus dorsi flap is an excellent alternative, particularly in the patient with a low body mass index.

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McCarthy CM, Lee CN, Halvorson EG, Riedel E, Pusic AL, Mehrara BJ, Disa JJ. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. Plast Reconstr Surg. 2012 Nov;130(5 Suppl 2):57S-66S. doi: 10.1097/PRS.0b013e31825f05b4.

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Salzberg CA, Dunavant C, Nocera N. Immediate breast reconstruction using porcine acellular dermal matrix (Strattice™): long-term outcomes and complications. J Plast Reconstr Aesthet Surg. 2013 Mar;66(3):323-8. doi: 10.1016/j.bjps.2012.10.015. Epub 2012 Nov 13.

Vardanian AJ, Clayton JL, Roostaeian J, et al. Comparison of implant-based immediate breast reconstruction with and without acellular dermal matrix. Plast Reconstr Surg. 2011; 128:403e–410e.

Summery of outcomes of studies comparing ADM and Non-ADM BR (11/34)

No further information

Reference:

Hanna KR, DeGeorge BR Jr, Mericli AF, Lin KY, Drake DB. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013 Jan;70(1):10-5. doi: 10.1097/SAP.0b013e31822f6765.

Summary of Characteristics and Conclusions of Studies Comparing ADM and Non-ADM Breast Reconstruction
(12/34)

No further information

Reference:

Hanna KR, DeGeorge BR Jr, Mericli AF, Lin KY, Drake DB. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013 Jan;70(1):10-5. doi: 10.1097/SAP.0b013e31822f6765.

Lipofilling (13/34)

Further information:

Link to fat modelling after implant-based reconstruction:

The use of lipomodelling by autologous fat transfer is increasing regarding the offer of an additional tool to refine breast reconstructive surgery. Several publications about the use after implant-based reconstruction are available. Bonomi et al. reported their findings regarding large-volume fat transfer in patients who have undergone autologous breast reconstruction with the latissimus dorsi (LD) flap and/ or implant-based reconstruction with subsequent lipomodelling for symmetrisation [Bonomi et al., 2013]. They retrospectively collected data on all patients who have undergone lipomodelling from October 2008 to October 2011. Fat was harvested using a low-negative pressure syringe method and centrifuged at 3000 r.p.m. for 3 min. The purified fat was injected in 1 mL increments into multilayered microtunnels, starting from deeper layers and moving to superficial layers in the subcutaneous tissue. Patient satisfaction was assessed using validated Picker questions in a face-to-face consultation during follow-up visits, and the results were documented in the case notes. Thirty-one patients underwent lipomodelling following autologous breast reconstruction using the LD flap and implant-based reconstruction. Three patients in the study group had bilateral lipomodelling, and one patient required 3 lipomodelling sessions. Seven patients required 2 sessions, and 21 patients required a single session to achieve bilateral symmetry. The mean volume of fat that was harvested was 396 mL, and the mean injected volume of fat was 247 mL. Four patients (1 breast cancer recurrence, 2 patients with fat necrosis and 1 patient with oil cysts) developed postoperative complications. Twenty-nine patients (93%) were satisfied with the postoperative cosmetic outcome. The authors conclude that large volumes of fat can be injected for sculpture optimization and for reshaping reconstructed breasts with improved softness and a natural feel.

The combination of fasciotomies and fat grafting seems to be an innovative concept in reconstructive surgery to improve the shape of the breast.

The management of breast deformities can be very difficult in the presence of breast shape retraction. Percutaneous fasciotomies, which release fibrous strings, can be a very useful tool for shape improvement in the recipient site for a fat

graft. Ho Quoc et al. have evaluated the efficacy of fasciotomies in association with fat grafting in breast surgery [Ho Quoc et al., 2013]. A retrospective chart review was conducted for 1000 patients treated with concurrent fasciotomies and fat grafting between January 2006 and December 2011. The recipient site was prepared with fasciotomies, and fat was harvested from other parts of the body using a low-pressure 10-mL syringe lipoaspiration system. Fat was centrifuged and injected into the breast for reconstruction or chest deformities. The postoperative appearance of the breast scars was scored by both the surgeon and the patient. Each complication was recorded, including instances of hematoma, infection, tissue wounds, scar healing, and fat necrosis. In this series of patients, for whom the primary indications for the procedure were sequelae of breast-conserving surgery after cancer, latissimus dorsi flap breast reconstruction, breast implant reconstruction, tuberous breast, Poland syndrome, and funnel chest, we recorded the following complications: 0.8% local infections (8/1000), 0.1% delayed wound healing that required medical care (1/1000), and 3% fat necrosis (31/1000). Fasciotomy scarring was considered minor by the patient in 98.5% of cases and by the surgeon in 99% of cases at 1 year postoperatively. The authors conclude that fat grafting is a safe and reliable technique that improves the aesthetic outcomes of breast surgery. Percutaneous fasciotomies provide excellent aesthetic results and an improvement in breast shape with no scarring.

Link to long-term safety:

There are reported concerns that the injection of fat may be involved in tumourigenesis, by stimulating angiogenesis and cell growth and thus dormant cancer cells [Lohsiriwat et al., 2011; Pearl et al., 2011; Fraser et al., 2011]. Current grafting techniques separate the destructed detritus and oil as well as blood and supernatant fluid. The final result is a cellular graft, which is an unpurified pool of various cells including adipocytes, preadipocytes, resident tissue cells and stromal stem cells, which include mesenchymal stem cells [Kumboeck et al., 2013]. The number of stem cells varies individually and dependent on the technique for liposuction, processing and grafting. Adipose derived stem cells are meanwhile well characterized, but little is known on how the transplanted or differentiated cells will react on a long-term or in cell-cell interaction with highly reproductive tissue or residual tumor cells. Moreover, human adipose tissue for lipografting is also a source of endothelial progenitor cells, which do not only exhibit MSC properties but were demonstrated to promote breast cancer progression and metastases in murine models.

By this, the oncologic risk should be evaluated by the impact on overall survival, disease-free survival, and local events, in comparison with the general population of breast cancer patients; and also by interferences on follow-up, which could increase the number of unnecessary biopsies, anxiety, and delay in the diagnosis of a true recurrences or new breast cancers [Vallejo et al., 2013].

Lipofilling has already been performed for breast reconstruction in over 2,000 patients in published trials from Europe and the United States. In addition, two systematic reviews have been published. In clinical series, until now, there has been no report of increasing risk of local events or metastasis in the follow-up of invasive breast cancer patients.

Delay et al. reported data on 734 lipomodelling procedures for breast cancer reconstruction who were followed up for 10 years and noted that 96% remained free of recurrence and 98% remained free of distant metastases 5 years after the procedure [Delay et al., 2009]. Rigotti et al. reported data from lipomodelling in 137 patients and found 9 local recurrences and 9 distant recurrences (11.7%) [Rigotti et al., 2010]. At the 5-year follow-up, 95.6% of the patients were free from local relapse and 97.7% were free from distant metastases. The multicenter study by Petit and colleagues reported data on 646 procedures in 513 patients with an overall oncological event rate of 5.6%, with a loco regional event rate of 2.4% [Petit et al., 2011]. Bonomi et al. reported one recurrence (3.7%), which occurred four years after the original cancer surgery and two years after the lipomodelling procedure [Bonomi et al., 2013].

Petit and colleagues, in a matched-cohort study, found a 1.5 percent rate of local events in a population of 513 breast cancer patients who underwent lipofilling [Petit et al., 2013]. This rate was similar to that of the general population.

However, particularly concerning was the higher local event rate (six times higher) in the subgroup of intraepithelial neoplasia patients compared with the control group. Lipofilling increased the risk of local events in women younger than 50 years, women with high-grade neoplasia, women with a Ki-67 proliferation index greater than 14, and women who had undergone quadrantectomy. Considering important limitations of this study (e.g., being a retrospective series, with different types of cancer treatments included, a relatively small number of patients analyzed, and follow-up limited to a median of 5 years after primary surgery), this subgroup analysis is considered only as exploratory by the authors, and no definitive conclusion could be drawn from this until now.

In patients with breast conserving surgery the risk of recurrence in the ipsilateral breast is up to 10% over 10 years and rises up to 16% over 20 years postoperatively. However the peak is within the first 5 years with almost 9% of relapse. In these recurrent cases ipsilateral, but different localization occurs in up to 31% and tumor progression to invasiveness was observed to be as high as 77%. The goal of breast conserving therapy is a good aesthetic result without complete resection

of all breast tissue, which can be achieved safely in many cases. So fat grafting might only be necessary for scar correction or to achieve improved symmetry. Therefore a longer period can be tolerated between breast surgery and correction through fat grafting. Based on the oncological outcome studies Krumboeck et al. would recommend an interval of at least 5 years before fat grafting after breast conserving therapy. Treatment should strictly be limited to the scar and subcutaneous tissue [Krumboeck et al., 2013].

Regarding patients with BRCA1/2-mutation these patients have an increased risk for developing breast cancer also on the contralateral site, Krumboeck et al. discourage from fat grafting in this population, even after complete tumor resection.

Link to technique:

Resorption rates ranging of fat grafts from 25% to 80% have been reported – 30% in normal postoperative tissue and 50% in tissue after local radiotherapy. Regarding the type of autologous fat grafting different techniques are available – e.g. fat grafts enriched with autologous adipose-derived stem cells (ASCs) or non-enriched fat grafts. Kolle et al. have published the results of a triple-blind, placebo-controlled trial to compare the survival of fat grafts enriched with autologous adipose-derived stem cells (ASCs) versus non-enriched fat grafts [Kolle et al., 2013]. Healthy participants underwent two liposuctions taken 14 days apart: one for ASC isolation and ex-vivo expansion, and another for the preparation of fat grafts. Two purified fat grafts (30 mL each) taken from the second liposuction were prepared for each participant. One graft was enriched with ASCs (20×10^6 cells per mL fat), and another graft without ASC enrichment served as a control. The fat grafts were injected subcutaneously as a bolus to the posterior part of the right and left upper arm according to the randomization sequence. The volumes of injected fat grafts were measured by MRI immediately after injection and after 121 days before surgical removal. The primary goal was to compare the residual graft volumes of ASC-enriched grafts with those of control grafts. 13 participants were enrolled, three of whom were excluded. Compared with the control grafts, the ASC enriched fat grafts had significantly higher residual volumes: 23.00 (95% CI 20.57–25.43) cm³ versus 4.66 (3.16–6.16) cm³ for the controls, corresponding to 80.9% (76.6–85.2) versus 16.3% (11.1–21.4) of the initial volumes, respectively ($p < 0.0001$). The difference between the groups was 18.34 (95% CI 15.70–20.98) cm³, equivalent to 64.6% (57.1–72.1; $p < 0.0001$). No serious adverse events were noted. By this, the procedure of ASC-enriched fat grafting had excellent feasibility and safety. Although the results present that the fat resorption rates are less ASC-enriched fat grafts cannot be recommended for breast cancer patients due to missing results for long-term safety.

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Petit JY, Rietjens M, Botteri E, et al. Evaluation of fat grafting safety in patients with intra epithelial neoplasia: A matched cohort study. *Ann Oncol*. 2013;24:1479–1484.

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Rigotti G, Marchi A, Stringhini P, et al. Determining the oncological risk of autologous lipoaspirate grafting for post-mastectomy breast reconstruction. *Ann Plast Surg* 2010;34:475–80.

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Follow-up results after lipofilling (14/34)

No further information

Reference:

Riggio E, Bordoni D, Nava MB. Oncologic surveillance of breast cancer patients after lipofilling. Aesthetic Plast Surg. 2013 Aug;37(4):728-35. doi: 10.1007/s00266-013-0166-5. Epub 2013 Jun 29.

Postmastectomy Pedicled Flap Reconstruction (15/34)

Further information and references:

Link to TRAM and DIEP:

When choosing autologous or heterologous reconstructive techniques, advantages or disadvantages have to be taken into consideration. The final choice has to be appropriate to the problem and the safest applicable technique should be chosen. Risk management has an important impact on complications and the aesthetic result.

As for the controversy between TRAM and DIEP-flap advocates the main argument in favour of the DIEP-flap is donor site morbidity. But the hernia rate of 2.1% in 280 published bilateral DIEP-flaps does not substantiate a better donor site morbidity. Brunnert series of 330 double pedicled TRAM flaps: 0.4% hernia rate. In addition, pedicled flaps can be performed in a muscle sparing technique as well.

Glyn Jones takes in his article: The pedicled TRAM flap in breast reconstruction. Clin Plastic Surg. 2007(34); 83-104 the following conclusion: Pedicled TRAM flap breast reconstruction remains the first choice for autologous reconstruction. And concerning the abdominal wall: over time, pedicled and free TRAM flap patients develop similar functional outcomes with little impact on the activities of daily living. Abdominal bulge and hernia rates appear to be independent of the type of flap harvested and may relate to the care with which repair has been undertaken as well as the quality of the fascia to be repaired. The exact mechanism for these observed differences has yet to be explained satisfactorily.

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Chevray PM, BR with SIEA flap: a prospective comparison with TRAM and DIEP flaps. PRS 2004, 114:5

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Roy LH et al., Technical variations of the bipediced TRAM flap in unilateral BR: effects of conventional versus microsurgical techniques of pedicle transfer on complication rates. PRS 2004, 114:2.

Williams JK, Carlson GW, Bostwick J III. et al., The effects of radiation after TRAM flap breast reconstruction. PRS 1997, 100:1153

Link to delay-Surgery:

To reduce the complication rate of pTRAM especially in high risk patients, a surgical delay has been suggested: the preoperative location and evaluation of perforating vessels and the variations of the DSEA a preoperative multidetector computed tomography angiography (MDCTA) is useful after performing a delay.

Reference:

Ribuffo D et al. Preoperative Angio-CT Preliminary study of the TRAM flap after selective vascular delay. Ann Plast Surg 2007 Dec;59(6):611-616.

Link to prophylaxis of deep vein thrombosis:

A multicenter retrospective review of consecutive TRAM flap cases identified 679 patients, 392 in the heparin-treated group and 287 in the control group. The post hoc sample sizes were adequate to detect a 5 percent difference in hematoma rate with 89 percent power at an alpha level of 5 percent ($p < 0.05$). Outcome measures of reoperative hematoma, deep

vein thrombosis, and pulmonary embolism were recorded. Reoperative hematoma occurred in 0.5 percent of patients in the heparin-treated group and 1.0 percent of patients in the control group; this difference was not statistically significant ($p = 0.66$). Thromboembolic events were detected at a low rate (0.8 percent in the heparin-treated group versus 1.4 percent in the untreated group; $p = 0.46$). The use of heparin for venous thrombotic prophylaxis did not increase the risk of reoperative hematoma after breast reconstruction with abdominal tissue. The authors propose a risk assessment that balances a statistical hematoma rate of 0.5 to 5 percent (clinically observed rate, 0.5 percent) with use of heparin prophylaxis against a rare (clinically observed rate, 1.4 percent) but morbid occurrence of thromboembolic complications when chemoprophylaxis is omitted.

Reference:

Liao EC, Taghinia AH, Nguyen LP, Yueh JH, May JW Jr, Orgill DP. Incidence of hematoma complication with heparin venous thrombosis prophylaxis after TRAM flap breast reconstruction. *Plast Reconstr Surg.* 2008 Apr;121(4):1101-7.
Links

Link to quilting sutures and drains in lat. dorsi reconstruction:

Latissimus dorsi (LD) flap breast reconstruction is associated with a high incidence of donor site seromas, despite the use of surgical drains. The aim of this study was to evaluate the use of donor site quilting sutures, as well as drains, on the incidence, volume and frequency of seroma aspiration. The trial randomized 108 women undergoing LD breast reconstruction to quilting procedures (54) or control group (52) for intention-to-treat analysis; two were excluded. Outcome measures were the incidence and volume of postoperative seroma. Secondary outcome measures included postoperative back pain, analgesic consumption, shoulder movement and duration of hospital stay. Quilting significantly reduced the overall incidence of seroma from 46 of 48 (96 per cent) to 43 of 52 (83 per cent) ($P = 0.036$), including the 38 women who had extended LD flap (with or without implants). There were further significant reductions in seroma volume ($P = 0.004$), frequency of aspiration ($P = 0.001$) and overall seroma volumes, including surgical drainage and symptomatic seromas ($P = 0.013$). Subset analyses for LD-implant (60 women) and extended LD (with or without implant) showed similar significance. Quilting did not affect back pain or compromise shoulder mobility. Quilting significantly reduced

overall seroma volumes after LD breast reconstruction including extended LD, and is recommended in combination with surgical drains.

Reference:

Daltrey I, Thomson H, Hussien M, Krishna K, Rayter Z, Winters ZE. Randomized clinical trial of the effect of quilting latissimus dorsi flap donor site on seroma formation. Br J Surg. 2006 Jul;93(7):825-30. [Links](#)

Link to pain management:

In this prospective, randomized, double-blind trial (Heller et al.), a dual-catheter continuous infusion pump system was placed in the muscle-sparing TRAM flap donor-site area in all patients. Bupivacaine (0.375%; continuous infusion pump group) or isotonic saline (control group) was infused at 4 ml/hour. All patients also had a patient-controlled anesthesia system delivering intravenous narcotics on demand. Pain scores, patient satisfaction, narcotic use, milestones of surgical recovery, and side effects of narcotics were compared between the two groups. Forty-eight patients were included in the study (23 continuous infusion pump patients and 25 control patients). The continuous infusion patients used less mean patient-controlled anesthesia narcotic during the first 2 postoperative days (78.0 mg versus 42.7 mg; $p = 0.019$) and transitioned earlier to oral narcotics than did control patients. Patients' overall pain satisfaction scores were significantly better in the continuous infusion group than in the control group. There were no significant differences between groups with regard to overall abdominal pain intensity scores, total narcotic use, length of hospitalization, incidence of narcotic side effects, or milestones of surgical recovery. The continuous infusion pump system appears to be a safe and effective method for postoperative donor-site pain management in TRAM flap breast reconstruction patients and should be considered for postoperative donor-site pain management. However, continuous infusion pump local anesthetic delivery to the muscle-sparing TRAM flap donor site did not eliminate narcotic use for pain control.

Reference:

Heller L, Kowalski AM, Wei C, Butler CE. Prospective, randomized, double-blind trial of local anesthetic infusion and intravenous narcotic patient-controlled anesthesia pump for pain management after free TRAM flap breast reconstruction. *Plast Reconstr Surg*. 2008 Oct;122(4):1010-8. Links

Link to prevention of seroma:

To systematically analyze the effectiveness of quilting of latissimus dorsi (LD) flap donor site in the prevention of seroma and related morbidities. All published studies comparing the effectiveness of quilting versus no-quilting of LD flap donor site in the prevention of seroma and related morbidities in patients undergoing breast reconstruction were analysed systemically. Five comparative studies on quilting versus no-quilting encompassing 440 patients were suitable for statistical analysis. There was no heterogeneity among trials. Therefore, in the fixed-effects model, quilting was effective in terms of reducing the incidence of donor-site seroma formation, reducing the average volume of the seroma, and reducing the total volume of drained seroma. In addition, quilting did not increase the risk of postoperative complications. Combined quilting and fibrin glue was also effective in reducing the average volume of the seroma and total drained volume of the seroma. Combination of quilting and glue did not influence the incidence of seroma formation at LD flap donor site and overall operative complications. Quilting of the LD flap donor site is helpful in reducing the incidence of seroma formation, reducing seroma volume, and reducing total drained seroma volume. Combined quilting and fibrin glue further enhances its effectiveness. Quilting with or without fibrin glue may be considered an option in patients undergoing LD flap breast reconstruction to control seroma-related morbidity. However, a major multicenter randomized controlled trial is required to achieve stronger and reliable evidence before recommending it as a routine procedure.

Reference:

Sajid MS, Betal D, Akhter N, Rapisarda IF, Bonomi R. Prevention of postoperative seroma-related morbidity by quilting of latissimus dorsi flap donor site: a systematic review. *Clin Breast Cancer*. 2011 Dec;11(6):357-63. Epub 2011 Jun 25.

Free Tissue Transfer(16/34)

Further information and references:

Link to TRAM and DIEP:

When choosing autologous or heterologous reconstructive techniques, advantages or disadvantages have to be taken into consideration. The final choice has to be appropriate to the problem and the safest applicable technique should be chosen. Risk management has an important impact on complications and the aesthetic result.

As for the controversy between TRAM and DIEP-flap advocates the main argument in favour of the DIEP-flap is donor site morbidity. But the hernia rate of 2.1% in 280 published bilateral DIEP-flaps does not substantiate a better donor site morbidity. Brunnert series of 330 double pedicled TRAM flaps: 0.4% hernia rate. In addition, pedicled flaps can be performed in a muscle sparing technique as well.

Glyn Jones takes in his article: The pedicled TRAM flap in breast reconstruction. Clin Plastic Surg. 2007(34); 83-104 the following conclusion: Pedicled TRAM flap breast reconstruction remains the first choice for autologous reconstruction. And concerning the abdominal wall: over time, pedicled and free TRAM flap patients develop similar functional outcomes with little impact on the activities of daily living. Abdominal bulge and hernia rates appear to be independent of the type of flap harvested and may relate to the care with which repair has been undertaken as well as the quality of the fascia to be repaired. The exact mechanism for these observed differences has yet to be explained satisfactorily.

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Allen RJ, et al. The in-the-crease inferior gluteal artery perforator flap for breast reconstruction. Plast Reconstr Surg. 2006; 118(2):333-9

Giordano et al. Latissimus dorsi free flap harvesting may affect the shoulder joint in long runs. Scan J Surg 2011; 100: 202-207

Garvey PB, Salavati S, Feng L, Butler CE. Perfusion-related complications are similar for DIEP and muscle-sparing free TRAM flaps harvested on medial or lateral deep inferior epigastric Artery branch perforators for breast reconstruction. Plast Reconstr Surg. 2011 Dec;128(6):581e-9e.

Anatomical studies suggest that the deep inferior epigastric artery (DIEA) medial branch perfuses more tissue across the midline than the lateral branch. The authors hypothesized that unilateral deep inferior epigastric perforator (DIEP) and muscle-sparing free transverse rectus abdominis musculocutaneous (TRAM) flaps based on medial branch perforators would have fewer perfusion-related complications. The authors evaluated consecutive DIEP or muscle-sparing TRAM free flaps definitively harvested from a single DIEA branch. Flaps were grouped by tissue volume (hemiflaps, cross-midline flaps, or total flaps). Primary outcome measures were fat necrosis and partial flap necrosis. Logistic regression was used to evaluate the association between patient and reconstruction characteristics and outcomes. There were 228 patients, with

120 medial (52.6 percent) and 108 lateral (47.4 percent) branch flaps. Mean follow-up was 33.2 months. Cross-midline flaps (79.8 percent) were the most common design. Medial and lateral branch flaps had similar rates of fat necrosis (8.3 percent and 13.0 percent, respectively; $p = 0.26$) and partial flap necrosis (3.3 percent and 2.8 percent, respectively; $p = 1.0$). There was no difference in the incidence of fat necrosis between DIEP and muscle-sparing free TRAM flaps (10.2 percent and 11.3 percent, respectively; $p = 0.81$) or in partial necrosis (3.2 percent and 2.8 percent, respectively; $p = 1.0$). Medial and lateral branch flap perfusion-related complications were also similar among the flap volume classifications. The authors suggest that surgeons base their decisions regarding DIEA branch harvest on the clinical assessment of perforator perfusion quality rather than relying on the theoretical benefit of medial branch perforator harvest. Clinical question/level of evidence: Therapeutic, III.

Conroy K, Malata CM. Epigastric hernia following DIEP flap breast reconstruction: Complication or coincidence? *J Plast Reconstr Aesthet Surg*. 2011 Jul 30. [Epub ahead of print]

Donor site hernias are a rare but well recognised complication of deep inferior epigastric perforator (DIEP) flap breast reconstruction but there are no reported cases of epigastric hernias after such surgery. We report three patients who developed symptomatic epigastric hernias within 2-8 months after discharge from follow-up. Patients who were referred to the Breast Plastic Surgery Clinic with symptomatic epigastric hernias following DIEP flap breast reconstruction were retrospectively reviewed. The three patients were aged between 50 and 70 years. Their mean BMI was 29 and none were smokers or diabetic. The incidences of other predisposing factors were: previous abdominal surgery (1/3), heavy lifting (2/3) and multiparity (2/3). They were successfully treated laparoscopically (2) or by open technique (1) confirming the CT scan findings. The aetiology of epigastric hernias is obscure in general. The association with DIEP flap harvest may be purely coincidental. However, it appears that abdominal flap harvest predisposed these patients to epigastric hernias. One or more of the following factors may have caused either weakness of the anterior abdominal wall or increased intraabdominal pressure: This series of 3 symptomatic epigastric hernias following DIEP flap breast reconstruction is interesting as it documents donor site morbidity at a site distant from the exact site of flap harvest; this subject merits further detailed investigation.

Momoh AO, Colakoglu S, Westvik TS, Curtis MS, Yueh JH, de Blacam C, Tobias AM, Lee BT. Analysis of Complications and Patient Satisfaction in Pedicled Transverse Rectus Abdominis Myocutaneous and Deep Inferior Epigastric Perforator Flap Breast Reconstruction. *Ann Plast Surg*. 2011 Jun 8. [Epub ahead of print]

The purpose of this study was to evaluate complications and patient satisfaction after pedicled transverse rectus abdominis myocutaneous (TRAM) and deep inferior epigastric perforator (DIEP) flap reconstruction at a single institution. There were 346 patients identified from 1999 to 2006 who underwent 197 pedicled TRAM and 217 DIEP flap reconstructions. Flap complication rates were similar between groups, whereas pedicled TRAM reconstructions had higher rates of abdominal bulge (9.5% vs. 2.3%, $P = 0.0071$) and hernias (3.9% vs. 0%, $P = 0.0052$). DIEP flap patients had significantly higher general satisfaction (81.7% vs. 70.2%, $P = 0.0395$), whereas aesthetic satisfaction was similar between groups. Furthermore, DIEP flap patients, particularly those undergoing bilateral reconstructions, were more likely to choose the same type of reconstruction compared with pedicled TRAM patients (92.5% vs. 80.7%, $P = 0.0113$). Understanding the differences in complications and satisfaction will help physicians and patients make informed decisions about abdominal-based autologous breast reconstruction.

Tamoxifen may increase the risk of microvascular flap complications. Surgeons should consider temporarily stopping the drug 28 days before microsurgical breast reconstruction.

Kelley BP Valero V Yi M Kronowitz SJ. *Plast Reconstr Surg*. 2012 Feb;129(2):305-14

Pedicled vs. Free Tissue Transfer(17/34)

Further information and references:

Link to TRAM and DIEP:

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Giordano et al. Latissimus dorsi free flap harvesting may affect the shoulder joint in long runs. Scan J Surg 2011; 100: 202-207

Giordano M, Kääriäinen J, Alavaikko T, Kaistila H, Kuokkanen: Latissimus dorsi free flap harvesting may affect the shoulder joint in Long runs. Scandinavian Journal of Surgery 100: 202–207, 2011

Background: the latissimus dorsi (Ld) muscle or myocutaneous flap is one of the most commonly used flaps and is believed to result in minimal donor-side morbidity. the impact on shoulder function from Ld removal is important due to the common nature of this procedure. previous studies have been performed after relatively short follow-up time and mostly after breast reconstruction. the purpose of this study was to objectively evaluate shoulder function years after latissimus dorsi muscle free flap operation. *Methods:* between 1998 and 2004, eight patients who underwent Ld-free flap for low- er limb (7) or head and neck (1) soft tissue reconstruction were enrolled in this study. scar, shoulder pain, function, mobility, stability and strength were evaluated and mea- sured by using the patient scar assessment Questionnaire (psaQ), the scar evaluation scale (ses) score, the american shoulder and elbow surgeons (ases) form, goniometer and

isokinetic tests. measurements of the operated sides were compared to the non-operated sides. *Results:* mean age was 54 ± 21 years and mean follow-up was 92.5 ± 36 months after surgery. mean psaQ was 73 (65%), mean ses score was 2 ± 1 . When comparing the operated sides to the unoperated sides, ases score was significantly lower in the operated side (76 versus 93, $p = 0.008$); the range of motion in active and passive endorotation, active extrarotation and active forward elevation were significantly reduced after surgery. operated side revealed a significant joint instability (3.6 versus 1.2, $p = 0.007$) using the ases form. isokinetic tests revealed that only intra-rotation strength was significantly reduced (35.74 newton-metre versus 42.7 newton-metre, $p = 0.03$) in the operated side. *Conclusion:* Ld harvesting can affect the function of the shoulder joint in the long run. reduced mobility, instability and weakness could be obtained with objective measurements. however, the results should be interpreted with caution because of the small sample size, internal controls and retrospective nature of this study. Key words: Latissimus dorsi flap; donor site; morbidity; shoulder function; joint; free flap

Scandinavian Journal of Surgery 100: 202–207, 2011 Latissimus dorsi free flap harvesting may affect the shoulder joint in Long runs. giordano¹, m. Kääriäinen², j. alavaikko², t. Kaistila², h. Kuokkanen² ¹Department of Surgery, Vaasa Central Hospital, Vaasa, Finland ²Department of Plastic Surgery, Tampere University Hospital, Tampere, Finland abstract

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Kääriäinen M, Giordano S, Kauhanen S, Lääperi AL, Mattila P, Helminen M, Kalimo H, Kuokkanen H. The significance of latissimus dorsi flap innervation in delayed breast reconstruction: a prospective randomized study-magnetic resonance imaging and histologic findings. *Plast Reconstr Surg.* 2011 Dec;128(6):637e-45e.

It is controversial whether surgical denervation of the thoracodorsal nerve should be performed in breast reconstruction with a myocutaneous latissimus dorsi flap. Denervation may prevent discomforting symptoms caused by muscle contraction, but the flap may also lose significant volume. The authors prospectively evaluated the influence of latissimus dorsi flap innervation on the latissimus dorsi muscle structure in delayed breast reconstruction. Between 2007 and 2008, 28 breast reconstructions were performed and divided randomly into the denervation group (surgical denervation by excision of 1 cm of thoracodorsal nerve, $n = 14$) and the intact group (thoracodorsal nerve saved intact, $n = 14$). Muscle biopsy specimens were taken during the operation and 6 months after reconstruction. Histologic (hematoxylin and eosin), immunohistochemical (human developmental, neonatal, slow, and fast myosin heavy chains), and morphometric analyses were performed. Magnetic resonance imaging of the breasts was performed 1 and 12 months after surgery. There was a significant decrease in type I and type II myofiber diameters from 0 to 6 months in both groups. Denervation caused more significant atrophy than disuse alone. However, there was no significant difference in flap thickness between groups that can be explained by more pronounced fatty tissue infiltration in the denervation group. The authors' data suggest that the volume and consistency of the flap remain more or less the same, regardless of whether the thoracodorsal nerve is cut or not. Thus, in their practice, the authors do not cut the nerve to save surgical time. Clinical question/level of evidence: Therapeutic, II.

Momoh AO, Colakoglu S, Westvik TS, Curtis MS, Yueh JH, de Blacam C, Tobias AM, Lee BT. Analysis of Complications and Patient Satisfaction in Pedicled Transverse Rectus Abdominis Myocutaneous and Deep Inferior Epigastric Perforator Flap Breast Reconstruction. *Ann Plast Surg.* 2011 Jun 8. [Epub ahead of print]

The purpose of this study was to evaluate complications and patient satisfaction after pedicled transverse rectus abdominis myocutaneous (TRAM) and deep inferior epigastric perforator (DIEP) flap reconstruction at a single institution. There were 346 patients identified from 1999 to 2006 who underwent 197 pedicled TRAM and 217 DIEP flap reconstructions. Flap complication rates were similar between groups, whereas pedicled TRAM reconstructions had higher rates of abdominal bulge (9.5% vs. 2.3%, $P = 0.0071$) and hernias (3.9% vs. 0%, $P = 0.0052$). DIEP flap patients had significantly higher general satisfaction (81.7% vs. 70.2%, $P = 0.0395$), whereas aesthetic satisfaction was similar between groups. Furthermore, DIEP flap patients, particularly those undergoing bilateral reconstructions, were more likely to choose the same type of reconstruction compared with pedicled TRAM patients (92.5% vs. 80.7%, $P = 0.0113$). Understanding the differences in complications and satisfaction will help physicians and patients make informed decisions about abdominal-based autologous breast reconstruction.

Flap-Implant Combination (18/34)

Further information and references:

Link to muscle contraction:

Between January 2002 and April 2006, 71 consecutive patients underwent delayed unilateral breast reconstructions with LD flap and sub-pectoral implant after mastectomy. All patients reporting discomforting signs and symptoms from muscle contraction in the reconstructed breast were included in this prospective study. Thirteen patients (18.3%) were selected and treated with BTX-A percutaneous local injections. Signs and symptoms were evaluated, after 4, 8 and 12 months, by the patients and by a panel of three physicians not involved in the study, using a five-point scale. During the study period all patients reported a decrease or disappearance of the signs and symptoms. After 12 months, 11 patients received three BTX-A infiltrations, demonstrating considerable improvements compared to the pre-treatment status. Wilcoxon matched pairs rank sum test showed a statistical difference between pre-treatment and post-treatment scores after 14 days ($P < 0.01$) and 12 months ($P < 0.001$). Our experience shows that muscular contraction deformities after breast reconstruction with a LD flap plus implant are not uncommon complications. The use of BTX-A infiltrations is an effective, not surgical, low cost and low risk procedure to treat these complications. It is an easy procedure to be performed on an outpatient basis with a temporary effect but safely repeatable and reproducible; it avoids hospitalisation or further surgical procedures and demonstrates tolerable latency with satisfactory outcomes.

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Figus A, Mazzocchi M, Dessy LA, Curinga G, Scuderi N. Treatment of muscular contraction deformities with botulinum toxin type A after latissimus dorsi flap and sub-pectoral implant breast reconstruction. J Plast Reconstr Aesthet Surg. 2008 Apr 12. [Epub ahead of print] Links

Perdikis G, Koonce S, Collis G, Eck D. Latissimus dorsi myocutaneous flap for breast reconstruction: Bad rap or good flap? *Eplasty* Oct 17, 2011 (Lit review)

Timing of Breast Reconstruction (19/34)

Further information and references:

See slide 3.

Zhong T, Hofer SO, McCready DR, Jacks LM, Cook FE, Baxter N. A Comparison of Surgical Complications Between Immediate Breast Reconstruction and Mastectomy: The Impact on Delivery of Chemotherapy-An Analysis of 391 Procedures.

To compare the postoperative complications after immediate breast reconstruction (IBR) versus mastectomy alone and to examine the impact on the delivery of chemotherapy.

In this prospective series, there were 391 consecutive women who underwent mastectomy (243 mastectomy alone and 148 mastectomy and IBR). The outcome measures were complications (within 3 months after surgery) and time to adjuvant chemotherapy.

Compared to the IBR group, patients in the mastectomy alone group were significantly older ($P < 0.0001$), smokers ($P = 0.007$) and less likely to have had previous radiation or lumpectomy ($P < 0.0001$). Overall, the complication rate was significantly greater in the IBR group than mastectomy alone (27.0% vs. 15.6%, $P = 0.009$). Univariate analyses revealed that mastectomy with IBR [odds ratio (OR) = 2, 95% confidence interval (CI) 1.21-2.30]; bilateral procedure (OR = 1.84, 95% CI 1.07-3.16); previous radiotherapy (OR = 2.4, 95% CI 1.29-4.47); and previous lumpectomy (OR = 1.84, 95% CI 1.11-3.03) were significant predictors of increased complications. With multivariable analysis, none of these variables were significantly associated with increased complications. 106 patients received adjuvant chemotherapy; median time from mastectomy to chemotherapy was 6.8 (0.71-15) weeks in the mastectomy alone group ($n = 96$) compared to 8.5 (6.3-11) weeks in the IBR group ($n = 10$) ($P = 0.01$).

Although the incidence of overall and major postoperative complications was higher after IBR than mastectomy alone, there were no significant relationships in the multivariable analysis. IBR was associated with a modest increase in time to chemotherapy that was statistically but not clinically significant.

A further retrospective study has investigated the association between IBR, complications and adjuvant chemotherapy delivery [Chang et al., 2013]. A retrospective analysis of patients in an academic breast service, who underwent mastectomy, with or without reconstruction, and received adjuvant chemotherapy was performed. Comparisons were made between 107 patients who received IBR and 113 who received mastectomy alone. Those receiving IBR were on average younger, with lower body mass index (BMI) and better prognoses. Overall complication rates were comparable (mastectomy alone: 45.1% versus IBR: 35.5%, $p = 0.2$). There was more return to surgery in the IBR group with 11.5% of tissue expanders requiring removal, whilst more seromas occurred in the mastectomy group. There was no significant difference in the median time to chemotherapy. In conclusion, the authors found no evidence that IBR compromised the delivery of adjuvant chemotherapy, although there was a significant incidence of implant infection. The finding that 10% of implants required removal was higher than expected. Most previous series have reported implant removal rates between 2 and 8% due to infection, extrusion and pain. Rey et al. [2005] reported a 2.9% implant removal rate in the group which received conventional adjuvant chemotherapy and 13% late removal rate after high dose adjuvant chemotherapy.

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- D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. *Cochrane Database Syst Rev*. 2011 Jul 6;(7):CD008674.
- Rey P, Martinelli G, Petit JY, Youssef O, De Lorenzi F, Rietjens M, et al. Immediate breast reconstruction and high-dose chemotherapy. *Ann Plast Surg* 2005;55:250-4.

Breast cancer is the most prevalent cancer in women and has a lifetime incidence of one in nine in the UK. Curative treatment requires surgery, and may involve adjuvant and neo-adjuvant therapy. In many women, post-mastectomy breast reconstruction is essential to restore body image and improve quality of life. Timing of reconstruction may be immediately at the time of mastectomy or delayed until after surgery. Outcomes such as psychosocial morbidity, aesthetics and complications rates may differ between the two approaches.

To assess the effects of immediate versus delayed reconstruction following surgery for breast cancer.

We searched the Cochrane Breast Cancer Group (CBCG) Specialised Register on 22 July 2010, MEDLINE from July 2008 to 26 August 2010, EMBASE from 2008 to 26 August 2010 and the WHO International Clinical Trials Registry Platform (ICTRP) on 26 August 2010.

Randomised controlled trials (RCTs) comparing immediate breast reconstruction versus delayed or no reconstruction in women in any age group and stage of breast cancer. We considered any recognised methods of reconstruction to one or both breasts undertaken at the same time as mastectomy or at any time following mastectomy.

Two review authors independently screened papers, extracted trial details and assessed the risk of bias in the one eligible study. We included only one RCT that involved that involved 64 women. We judged this study as being at a high risk of bias. Post-operative morbidity and mortality were not addressed, and secondary outcomes of patient cosmetic evaluations and psychosocial well-being post-reconstruction were inadequately reported. Based on limited data there was some, albeit unreliable, evidence that immediate reconstruction compared with delayed or no reconstruction, reduced psychiatric morbidity reported three months post-operatively. The current level of evidence for the effectiveness of immediate versus delayed reconstruction following surgery for breast cancer was based on a single RCT with methodological flaws and a high risk of bias, which does not allow confident decision-making about choice between these surgical options. Until high quality evidence is available, clinicians may wish to consider the recommendations of relevant guidelines and protocols. Although the limitations and ethical constraints of conducting RCTs in this field are recognised, adequately powered controlled trials with a focus on clinical and psychological outcomes are still required. Given the paucity of RCTs in this subject, in future versions of this review we will look at study designs other than RCTs specifically good quality cohort and case-control studies.

D'Souza N, Darmanin G, Fedorowicz Z. Immediate versus delayed reconstruction following surgery for breast cancer. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD008674.

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Link to immediate free autologous breast reconstruction after neoadjuvant therapy:

Previous published studies evaluating the outcomes of immediate free flap breast reconstruction following NC and timing of adjuvant treatment have reported conflicting results.

Albino et al. [Albino et al., 2010] compared outcomes in patients who undergone NC prior to immediate breast reconstruction, including 47 patients and 29 controls who had undergone free flap breast reconstruction. The study found that NC was significantly associated with complications, with a nearly a fivefold increase in total complications measured. Azzawi et al. [Azzwai et al., 2010] compared outcomes in patients including 28 immediate free flap breast reconstructions following NC with 36 comparator reconstructions. Overall complications were not significantly different between all patients who had received NC and those who had not, but the study included pedicled flaps, pedicled flaps with implants, and implant only reconstructions. The rate of minor complications in the group receiving NC was almost twice that of the control group although this was not significantly different. No delay in adjuvant therapy was found. Mehrara et al. [Mehara et al., 2010] reported outcomes in a study of 1195 free flap breast reconstructions in 952 patients, 694 of which were immediate reconstructions. Seventy patients had NC, defined as chemotherapy administered less than or equal to 6 weeks before reconstruction, and NC was an independent predictor of complications, associated with wound-healing problems at the donor site and fat necrosis.

The following prospective trial has been reported by Schaverien and Munnoch [2013]: A prospective study of immediate free flap breast reconstructions comparing patients who received NC with those who did not was conducted in a single specialist regional unit. Eighty-seven patients (95 flaps) were included in the study, 30 of which (35 flaps) received NC followed by free flap breast reconstruction. Twenty patients in the NC group had one or more complications compared with 37 patients in the control group ($p = 0.87$). Nine patients in the NC group had more than one complication compared with 11 patients in the control group, although this difference was not significant ($p = 0.26$). Both obesity ($p = 0.016$) and current cigarette smoking ($p = 0.014$) were significantly associated with the occurrence of any complication in patients who had received NC. Adjuvant radiotherapy was delayed in 3 patients in the NC group, and adjuvant chemotherapy was delayed in 3 control patients ($p = 1$). The mean preoperative haemoglobin was significantly lower in the NC group than in the control group ($p = 0.00037$), although there was no significant difference in blood transfusion requirements.

The authors conclude that patients undergoing immediate autologous breast reconstruction following NC have a similar complication and reoperation rate to patients not receiving NC. Preoperative blood haemoglobin level was found to be significantly lower following NC and postoperative blood transfusion triggers should take this into account.

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Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction (20/34)

Further information and references:

[Link to safety and preservation of NAC \(nipple areola complex\):](#)

SSM is considered a safe alternative to MRM especially if a BR is incorporated. SSM is widely practised in major centers which manage large numbers of breast cancer but anxiety still exists over the safety of SSM both from oncological and aesthetic points of view. Agrawal et al. have reviewed the literature to date in SSM and summarized and discussed the current evidence [Agrawal et al., 2013]. Studies were identified by an online search of the English language literature in the PubMed database till April 2012 followed by an extensive review of bibliographies from relevant articles. There is abundance of evidence with regards to the safety of SSM both oncologically and aesthetically especially in immediate breast reconstruction. The use of SSM technique broadens the repertoire of oncoplastic techniques and at the same time facilitates such techniques by preserving patient's native skin and anatomical landmarks. SSM is a safe technique providing better cosmetic outcome without compromising oncological safety as per the current evidence. However, prospective data collection of its application in various newer types of reconstructions, and continuing long-term follow-up of current data series would be prudent to evaluate long-term outcomes.

Preservation of a skin envelope and, in an increasing number, the NAC does not put the patient at risk. Latter is possible in a more peripheral location of the tumor and is validated by intraoperative frozen section. All of the glandular tissue has to be removed. This may cause healing problems due to reduced blood supply as a result of heavy smoking or preoperative RT.

From March 2002 to November 2006, 579 cases (in 570 patients) of NSM (nipple sparing mastectomy) were performed for carcinoma. The median follow up time was 19 months (Range: 1-60). The subcutaneous mastectomy was performed through an incision removing a portion of the skin overlying the tumour. An extemporaneous histological examination was performed on the retroareolar glandular tissue. If the histology was positive the patient was not considered eligible. Then an intraoperative radiotherapy with electrons (ELIOT) of 16 Gy in one shot was delivered on the NAC area. An immediate

breast reconstruction was done using implants in most cases and in several cases a musculocutaneous flaps, usually in large breast. The number of local recurrences was recorded and the correlation between their occurrence and the clinical and histological criteria were analysed using the Gray test statistical method in a competing framework. In 516 cases the negative retroareolar frozen section biopsy was confirmed by the final histology, while in 63 cases, the final histology showed foci of carcinoma. Seven out of these 63 cases underwent a secondary NAC removal. In the 56 cases which preserved areolas the authors did not observe any local recurrence after 19 months follow up. The probability of retro areola positive histology increases with the tumour size, and was not related to the nodal status. The rate of local relapses was 0.9% per year. They didn't find any significant difference in the local relapse rate according to different patient's and tumour's features. Most relapses were located close to the tumour bed but never in the NAC area. This study confirms that the local recurrence rate in the NSM completed with local radiotherapy on the NAC is not higher than the usual rate observed in the literature and the preservation of the NAC does not increase the risk. The absence of local recurrence in the region where a portion of glandular tissue has been purposely preserved is a good argument in favour of ELIOT (Petit et al.).

Gerber et al. (2003) selected retrospectively 286 patients with a breast cancer observed preoperatively 2 cm distant from the NAC. From 246 patients follow-up data could be observed. Intraoperative a frozen section of the retroareolar region was performed. The result of the frozen section was the resection of the NAC in 61 patients despite an originally planned SSM. An IBR using latissimus dorsi flap with an implant or TRAM was performed in these cases. 51 patients got a modified mastectomy. After a median follow-up of 59 months the patients with a SSM had a local recurrence rate of 5.4% and the patients with a MME of 8.2%. Only one patient of the SSM group suffered from a retromammary recurrence.

Crowe et al. (2004) planned in 44 patients in 54 breasts to perform a SSM. In 6 of these patients a MME had to be performed as a result of the intraoperative frozen section. The remaining 48 patients with a SSM had a good postoperative result with well perfused NAC. In 3 patients they observed partial necroses.

Vaughan et al. identified 206 patients who underwent 210 skin-sparing mastectomies with immediate reconstruction from 1998 to 2006 in our database. Eleven patients had local recurrences (5.3%). Nine developed in the quadrant of the corresponding primary tumor. There were no significant differences between patients who recurred and those who did not with respect to tumor size/stage, margin status, estrogen receptor/progesterone receptor/Her2neu status, lymph node metastases, or radiation therapy ($P > .05$). Patients with grade 3 invasive tumors or high-grade ductal carcinoma in situ were more likely to recur than patients with grade 1 or 2 invasive tumors or low- or intermediate-grade ductal carcinoma in

situ ($P = .0035$). Those patients who recurred had a significantly decreased overall survival compared to patients who did not recur ($P = .0006$). Skin-sparing mastectomy and immediate reconstruction has a low local recurrence rate. Recurrences occur most commonly in the same quadrant as the primary tumor and treatment approaches include surgery, chemotherapy, and radiation therapy. Local recurrence portends a poorer overall survival.

Two-hundred and sixteen patients, mean age of 52.8 (29-81) years with primary unilateral breast cancer, not suitable for partial mastectomy because of large ($>3\text{cm}$) or multifocal carcinoma, underwent NSM, a single procedure lasting about 1h 30min, between December 1988 and September 1994 (Benediktsson et al.) . Lymph node metastases were found in 40.3% of the patients, and 47 patients received radiotherapy (RT) postoperatively. All patients were monitored for at least 11.6 years or as long as they lived. Median follow-up was 13 years. The end-points were locoregional recurrence (LRR) or distant metastases (DM) as first events, disease-free survival (DFS) and overall survival (OS). Specificity at frozen section from sub-areolar tissues was 98.5%. LRR occurred in 52 patients and DM in 44 patients. DFS was 51.3% and OS was 76.4%. The frequency of LRR was 8.5% among irradiated and 28.4% among non-irradiated patients ($p=0.025$). These results compare well with results after conventional mastectomy in other trials. All patients were monitored for at least 6 years after the occurrence of LRR, finding 5 years freedom from further LRR or DM of 60% and OS of 82%. NSM is an oncologically safe procedure and could be offered to most patients with breast cancer unsuitable for sector resection only. RT effectively lowers the frequency of LRR. The occurrence of LRR after this operation does not significantly affect OS.

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Vaughan A, Dietz JR, Aft R, Gillanders WE, Eberlein TJ, Freer P, Margenthaler JA. Scientific Presentation Award. Patterns of local breast cancer recurrence after skin-sparing mastectomy and immediate breast reconstruction. Am J Surg. 2007 Oct;194(4):438-43.

Link to higher quality of life:

Between 2004 and 2006, 310 women with NAC preservation and 143 patients with successive NAC reconstruction were mailed the questionnaire at follow-up 1 year after definitive complete breast reconstruction surgery. 256 questionnaires was available. The results showed significant differences in favour of the NAC sparing group regarding body image (difficulty in looking at themselves naked and being seen naked by their partners after surgery, $P = 0.001$ and $P = 0.003$, respectively); regarding satisfaction with the appearance of the nipple ($P < .0001$) and with the sensitivity of the nipple ($P = 0.001$); regarding the feeling of mutilation ($P = 0.003$). NAC sparing in mastectomy has a positive impact on patient satisfaction, body image and psychological adjustment (Didier et al.).

Link to skin incisions:

The periareolar incision provides good access to the breast tissue. On the other hand will the incision in the inframammary fold provide more undisturbed blood supply to the NAC and less damage to the tissue of the areola. SSM has to be combined with a reconstructive method to preserve shape and volume and prevent shrinkage postoperatively.

Die Nekroserate ist am geringsten, wenn ein radiärer Schnitt durch den MAK geführt wird und wenn mit autologem Gewebe rekonstruiert wurde. Zu diesem Ergebnis kommt eine prospektive outcome-Studie (Wijayanayagam et al.), in der an einem universitären Zentrum 64 hautsparende Mastektomien an 43 Frauen durchgeführt wurden. Darunter waren prophylaktische Mastektomien (n=29), invasive Karzinome (n=24) und präinvasive Karzinome (n=11). Es wurde präoperativ ein MRT durchgeführt und es wurden die Patientinnen ausgewählt mit einem Mammakarzinom, das weiter als 2 cm vom MAK entfernt war. Das Retroareolärgewebe wurde pathologisch besonders aufgearbeitet (Serienschnitte). Die Schnittführungen waren periareolär, inframammär, wie bei Reduktion/Mastopexie, Inzisionen (Kreuzform) durch den MAK und radiäre Schnittführungen. Es wurde immer eine Sofortrekonstruktion mit autologem und heterologem Gewebe (Implantate, Expander) durchgeführt. Ein okkultes DCIS wurde in 3% der Patientinnen histologisch beschrieben. Komplikationen waren Implantatverlust, Hautnekrosen, Infektionen. Kein Rezidiv.

Blechman et al. have reviewed 55 consecutive NSMs performed through a lateral IMF incision with immediate implant-based reconstruction, with or without tissue expansion, between June 2008 and June 2011 [Blechman et al., 2012]. Mean patient age was 46 years, and mean follow-up time was 12 months. Twelve mastectomies (22%) were therapeutic, and the remaining 43 (78%) were prophylactic. Mastectomy flap necrosis, requiring operative debridement, occurred in two breasts (4%), both in the same patient. One of these breasts required a salvage latissimus dorsi myocutaneous flap to complete the reconstruction. Three nipples (6%) required office debridement for partial necrosis and operative reconstruction later. No patient had complete nipple necrosis. No statistically significant differences existed between therapeutic and prophylactic mastectomies for developing partial skin and/or nipple necrosis ($p = 0.35$). Three episodes (5%) of cellulitis occurred, which responded to antibiotics without the need for explantation. The authors conclude that excellent results can be achieved with immediate implant-based reconstruction of NSM through a lateral IMF incision. NAC survival is reliable, and complication rates are low.

Moreover, SSM with preservation of the NAC is also feasible after mastopexy or reduction mammoplasty. Vaughn et al. reviewed the outcomes of TSSM in 11 patients who underwent 21 TSSM procedures at our institution between 2008 and 2011 [Vaughn et al. 2013]. All patients had undergone previous breast surgery including reduction mammoplasty (7 breasts), mastopexy (4 breasts), augmentation (3 breasts), and combined mastopexy-augmentation (7 breasts). Incisions from previous breast surgery included circumareolar (11 cases) and Wise pattern (10 cases) incisions. All patients underwent TSSM through an inframammary incision followed by immediate tissue expander reconstruction and subsequent implant exchange. Patient demographics, previous breast surgery details, tumor and treatment characteristics, and postoperative complications were reviewed. Mean patient age was 43 years (range, 35-53 years) and mean body mass index was 24 kg/m² (range, 19-32 kg/m²). Mean follow-up was 10.2 months (range, 3-20 months). Indications for TSSM included prophylactic risk reduction in 10 cases, in situ cancer in 2 cases, and invasive cancer in 9 cases. Mean time from previous breast surgery to mastectomy was 6.9 years (range, 6 months-26 years). Major complications requiring operative reintervention included 1 (4.8%) case of cellulitis requiring expander removal and 2 (9.5%) cases of wound breakdown requiring operative closure. There were no complications involving the NAC. The authors conclude that total skin-sparing mastectomy with immediate reconstruction can safely be performed in patients who have undergone previous breast surgery involving circumareolar incisions. The preferred technique in this group of patients is to perform TSSM through an inframammary incision with 2-stage expander-implant reconstruction to minimize NAC ischemia and subsequent complications.

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SSM / Nipple SM (21/34)

No further information

No references

Bilateral Risk Reducing Mastectomy in healthy women (RRBM) (22/34)

Further information and references:

Siehe auch ASCO/SSO Review 2006: Vol24: 4642 ff

The prophylactic mastectomy is a preventive option for patients with a high risk of BC-development. Volume replacement and preservation of a natural breast shape are a substantial part of the therapeutical and surgical strategy. The choice of technique has to be made individually as usual. Alternative systemic options and advanced imaging for screening purposes (MRI) must be discussed with the patient.

Link to reduction of incidence of bc in high risk patients:

Cochrane analyses published 2004: The primary objective was to determine whether prophylactic mastectomy reduces death from any cause in women who have never had breast cancer and in women who have a history of breast cancer in one breast. The secondary objective was to examine the effect of prophylactic mastectomy on other endpoints including breast cancer incidence, breast cancer mortality, disease-free survival, physical morbidity, and psychosocial outcomes. Electronic searches were performed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Cancerlit, and the Science Citation Index. Inclusion criteria were studies in English of any design type including randomized or nonrandomized controlled trials, cohort studies, case-control studies, and case series with at least ten participants. Participants included women at risk for breast cancer in at least one breast. Interventions included all types of mastectomy performed for the purpose of preventing breast cancer, including subcutaneous mastectomy, total or simple mastectomy, modified radical mastectomy, and radical mastectomy. Information on patients, interventions, methods, and results were extracted by at least two independent reviewers. Methodological quality was assessed based on how well each study minimized potential selection bias, performance bias, detection bias, and attrition bias. Data for each study were summarized descriptively; quantitative meta-analysis was not feasible due to heterogeneity of study designs and insufficient reporting. Data were analyzed separately for bilateral prophylactic mastectomy (BPM) and contralateral

prophylactic mastectomy (CPM). Twenty-three studies, including more than 4,000 patients, met inclusion criteria. No randomized or nonrandomized controlled trials were found. Most studies were either case series or cohort studies. All studies had methodological limitations, with the most common source of potential bias being systematic differences between the intervention and comparison groups that could potentially be associated with a particular outcome. Thirteen studies assessed the effectiveness of BPM. No study assessed all-cause mortality after BPM. All studies reporting on incidence of breast cancer and disease-specific mortality reported reductions after BPM. Nine studies assessed psychosocial measures; most reported high levels of satisfaction with the decision to have prophylactic mastectomy (PM) but more variable satisfaction with cosmetic results. Only one study assessed satisfaction with the psychological support provided by healthcare personnel during risk counseling and showed that more women were dissatisfied than satisfied with the support they received in the healthcare setting. Worry over breast cancer was significantly reduced after BPM when compared both to baseline worry levels and to the groups who opted for surveillance rather than BPM. Three studies reported body image/feelings of femininity outcomes, and all reported that a substantial minority (about 20%) reported BPM had adverse effects on those domains. Six studies assessed contralateral prophylactic mastectomy. Studies consistently reported reductions in contralateral incidence of breast cancer but were inconsistent about improvements in disease-specific survival. Only one study attempted to control for multiple differences between intervention groups, and this study showed no overall survival advantage for CPM at 15 years. Two case series were exclusively focused on adverse events from prophylactic mastectomy with reconstruction, and both reported rates of unanticipated re-operations from 30% to 49%. While published observational studies demonstrated that BPM was effective in reducing both the incidence of, and death from, breast cancer, more rigorous prospective studies (ideally randomized trials) are needed. The studies need to be of sufficient duration and make better attempts to control for selection biases to arrive at better estimates of risk reduction. The state of the science is far from exact in predicting who will get or who will die from breast cancer. By one estimate, most of the women deemed high risk by family history (but not necessarily BRCA 1 or 2 mutation carriers) who underwent these procedures would not have died from breast cancer, even without prophylactic surgery. Therefore, women need to understand that this procedure should be considered only among those at very high risk of the disease. For women who had already been diagnosed with a primary tumor, the data were particularly lacking for indications for contralateral prophylactic mastectomy. While it appeared that contralateral mastectomy may reduce the incidence of cancer in the contralateral breast, there was insufficient evidence about whether, and for whom, CPM actually improved survival. Physical morbidity is not uncommon following PM, and many women underwent unanticipated re-operations

(usually due to problems with reconstruction); however, these data need to be updated to reflect changes in surgical procedures and reconstruction. Regarding psychosocial outcomes, women generally reported satisfaction with their decisions to have PM but reported satisfaction less consistently for cosmetic outcomes, with diminished satisfaction often due to surgical complications. Therefore, physical morbidity and post-operative surgical complications were areas that should be considered when deciding about PM. With regard to emotional well-being, most women recovered well postoperatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures; exceptions also have been noted. Of the psychosocial outcomes measured, body image and feelings of femininity were the most adversely affected.

Reference:

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(BR), mutation status, age at PM and preoperative imaging examination results were extracted from the medical records, and analyzed separately for women without (unaffected, n = 177) and with a BC history (affected, n = 181). No primary BCs occurred after PM (median follow-up 4.5 years). In one previously unaffected woman, metastatic BC was detected almost 4 years after PM (primary BC not found). Median age at PM was younger in unaffected women ($P < .001$), affected women more frequently were 50% risk carriers ($P < .001$). Unexpected (pre)malignant changes at PM were found in 3% of the patients (in 5 affected, and 5 unaffected women, respectively). In 49.6% of the women opting for BR one or more complications were registered, totaling 215 complications, leading to 153 surgical interventions (71%). Complications were mainly related to cosmetic outcome (36%) and capsular formation (24%). The risk of developing a primary BC after PM remains low after longer follow-up. Preoperative imaging and careful histological examination is warranted because of potential unexpected (pre)malignant findings. The high complication rate after breast reconstruction mainly concerns cosmetic issues.

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Isern AE, Loman N, Malina J, Olsson H, Ringberg A. Histopathological findings and follow-up after prophylactic mastectomy and immediate breast reconstruction in 100 women from families with hereditary breast cancer. *Eur J Surg Oncol*. 2008 Oct;34(10):1148-54. Epub 2008 Apr 23. [Links](#)

Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, van Geel AN, Tilanus-Linthorst MM, Bartels CC, Tan M, Meijers-Heijboer HE, Klijn JG, Seynaeve C. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol*. 2007 Dec;14(12):3335-44. Epub 2007 May 31. [Links](#)

Link to patients's satisfaction and counseling:

The aim of this retrospective study was to find areas for future surgical improvements to optimize patient satisfaction with the aesthetic result after bilateral prophylactic mastectomy and immediate breast reconstruction with implants. Nipple-areola complexes were reconstructed. Twenty-four consecutive and standardized operated women were included. The

follow-up time was an average of 5.4 (range: 2.4-10.2) years. The outcome in terms of breast symmetry, size, and firmness were measured with objective and subjective methods, and results were compared to those from a control group of 24 women. Patient satisfaction was evaluated with a questionnaire. Main findings were that the overall aesthetic result was regarded as good in both objective and subjective evaluations and that breast symmetry in patients was as common as in the control group, but reconstructed breasts were firmer. Twenty of 24 patients thought that the aesthetic result exceeded their expectations, and 22/24 would recommend this kind of breast reconstruction to another woman. In contrast with the predictions of plastic surgeons, patients were most dissatisfied with the nipple-areola reconstruction. The overall aesthetic result after bilateral prophylactic mastectomy and immediate breast reconstruction with implants was good and symmetrical. Patient satisfaction with nipple-areola reconstruction was only moderate. The results emphasize the importance of a preoperative discussion with the patient regarding whether to keep or reconstruct the nipple-areola complex while planning a prophylactic mastectomy.

Sixty-one women underwent prophylactic mastectomy and immediate breast reconstruction in Malmö, Sweden (Isern et al.), between 1995 and 2003. Forty women underwent bilateral prophylactic mastectomy and immediate reconstruction. Ten of these had a previous breast cancer diagnosis. Twenty-one women underwent contralateral prophylactic mastectomy and immediate reconstruction after a previous breast cancer. Fifty-four of the women (89%) were evaluated clinically for aesthetic results and complications. Patient satisfaction and quality of life were evaluated with one study-specific and two standardised health-related questionnaires administered at time of clinical follow-up. Median follow-up time was 42 months (range 7-99 months). The position of the reconstructed breasts was judged as satisfactory in 77% of breasts. Symmetry in relation to the midline was adequate in 89% of breasts. A capsular contracture grade III according to Baker and indentation tonometry was observed in 1% of breasts (1/104). The complication rate was 18% (7% early and 11% late). Secondary corrections were carried out in 11% of breasts. The study-specific questionnaire revealed a high degree of satisfaction. No woman regretted the procedure, and all women would have chosen the same type of surgery again. An age-stratified comparison of Swedish women using the Short Form 36 Health Survey Questionnaire (SF-36) questionnaire was carried out for this study. The study population scores were high, suggesting that prophylactic mastectomy and immediate reconstruction on both physical and psychological issues in this retrospective study had no negative effect. Also, the Hospital Anxiety and Depression Scale (HAD) questionnaire did not suggest any increased anxiety or depression among the patients. Prophylactic mastectomy and immediate breast reconstruction in women at risk of hereditary breast

cancer may be carried out with a satisfactory aesthetic outcome and an acceptable rate of complications comparable to those in other studies, and does not in itself seem to be associated with a decreased quality of life.

The authors (Bresser et al.) conducted a retrospective study using a short self-report questionnaire administered to 114 genetically predisposed women who underwent prophylactic mastectomy and breast reconstruction mainly by subpectorally implanted silicone prostheses performed at one institution. The median follow-up time between prophylactic mastectomy/breast reconstruction and completion of the questionnaire was 3 years. Sixty percent of all participants were satisfied with the result of prophylactic mastectomy/breast reconstruction. Satisfaction was significantly and negatively correlated with perceived lack of information, experienced complications, ongoing complaints, whether or not the reconstructed breasts feel "like your own," and not choosing this type of breast reconstruction again. Adverse effects in the patient's sexual relationship were strongly correlated with perceived lack of information, discrepant expectations, ongoing complaints and limitations, whether or not the reconstructed breasts feel "like your own," altered feelings of femininity, partner's negative perception on femininity and sexuality, and not choosing this type of breast reconstruction again.

CONCLUSIONS: A majority of women would choose the procedure again, but adverse effects and untoward changes in the perception of the sexual relationship need to be addressed in the counselling of women at high risk, to optimize an informed choice and enable adequate adjustment postoperatively.

Although prophylactic mastectomy (PM) has proven to be the most effective method to reduce the risk of breast cancer in high-risk women, there is a need for further education of physicians regarding the possibilities and advantages of PM. Knowledge about breast/ovarian cancer genetics is likely to be associated with being more positive about PM, because the high risks of cancer as well as the limitations of breast cancer screening are most likely better understood by knowledgeable practitioners [Den Heijer et al., 2013]. It has been shown that the uptake of PM varies significantly across countries, with Dutch and United Kingdom (UK) studies reporting remarkably high uptakes (33–50%). One study among newly diagnosed breast cancer patients demonstrated that physician's recommendation influenced women's decision for PM. Julian-Reynier [2000] reported that only 18.7% of physicians involved in breast cancer management found PM an acceptable procedure in women with a BRCA1/2 mutation.

Den Heijer et al. presented the attitudes towards PM among physicians in France, Germany, the Netherlands and the United Kingdom (UK) [Den Heijer et al., 2013]. An international sample of 1196 general practitioners (GPs) and 927

breast surgeons (BS) were surveyed using a mailed questionnaire. Only 30% of the French and 27% of the German GPs were of opinion that PM should be an option for an unaffected female BRCA1/2 mutation carrier, as compared to 85% and 92% of the GPs in the Netherlands and UK, respectively. Similarly, 78% of the French and 66% of the German BS reported a positive attitude towards PM, as compared to 100% and 97% of the BS in the Netherlands and UK, respectively. In the whole sample of GPs, a positive attitude towards PM was associated with country of residence, being female, and having more knowledge of breast/ovarian cancer genetics, while among BS there was a positive association with country of residence and having more knowledge of breast/ovarian cancer genetics as well, and, in addition, with a higher number of newly diagnosed breast cancer patients last year. These results demonstrated the international variations in the attitude towards PM among physicians.

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Bresser PJ, Seynaeve C, Van Gool AR, Brekelmans CT, Meijers-Heijboer H, van Geel AN, Menke-Pluijmers MB, Duivenvoorden HJ, Klijn JG, Tibben A. Satisfaction with prophylactic mastectomy and breast reconstruction in genetically predisposed women. *Plast Reconstr Surg*. 2006 May;117(6):1675-82; discussion 1683-4. Links

Den Heijer M, van Asperen CJ, Harris H, Nippert I, Schmidtke J, Bouhnik AD, Julian-Reynier C, Evans DG, Tibben A. International variation in physicians' attitudes towards prophylactic mastectomy - comparison between France, Germany, the Netherlands and the United Kingdom. *Eur J Cancer*. 2013 Sep;49(13):2798-805. doi: 10.1016/j.ejca.2013.04.025. Epub 2013 May 18.

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Julian-Reynier C, Eisinger F, Moatti JP, Sobol H. Physicians' attitudes towards mammography and prophylactic surgery for hereditary breast/ovarian cancer risk and subsequently published guidelines. *Eur J Hum Genet* 2000;8(3):204–8.

Types of Risk Reducing Mastectomy in healthy women (RRBM) (23/34)

Further information and references:

Siehe auch ASCO/SSO Review 2006: Vol24: 4642 ff

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to problems with reconstruction); however, these data need to be updated to reflect changes in surgical procedures and reconstruction. Regarding psychosocial outcomes, women generally reported satisfaction with their decisions to have PM but reported satisfaction less consistently for cosmetic outcomes, with diminished satisfaction often due to surgical complications. Therefore, physical morbidity and post-operative surgical complications were areas that should be considered when deciding about PM. With regard to emotional well-being, most women recovered well postoperatively, reporting reduced cancer worry and showing reduced psychological morbidity from their baseline measures; exceptions also have been noted. Of the psychosocial outcomes measured, body image and feelings of femininity were the most adversely affected.

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Concerning the contralateral prophylactic mastectomy (CPM) in women with breast cancer, the satisfaction of patients can be high with this kind of procedure. Soran et al. have evaluated decision making and factors influencing women's long-term satisfaction with CPM [Soran et al., 2013]. Descriptive analysis was used to analyze the results of the designed questionnaire approved by an Institutional Review Board. The authors searched their institutional cancer registry for patients diagnosed with breast cancer between 2000 and 2010. The studied time frame was of significance as this study was the first to measure response rate in questions examining patient satisfaction for >1 year after undergoing CPM. The questionnaire was mailed to all consented participants to examine factors contributing to the choice of CPM and postoperative satisfaction. Of the 206 women included in the study, 147 were aged up to 50 years. Majority of women who underwent CPM in this cohort was with a bachelor's degree or higher, married or partnered women, and women earning >\$60,000/y. Almost all women were "happy with overall surgery" and would recommend CPM to other patients. Psychological factors, such as fear of recurrence, were more commonly associated with the decision for CPM in patients with invasive carcinoma. Opinions of partners, relatives, friends, and physicians further contributed to the decision to

undergo surgery. The availability of reconstruction was also an influential factor in the overall decision. The authors conclude the majority of our study participants experienced long-term satisfaction with the surgical procedure of CPM.

Link to Breast sensibility after bilateral risk-reducing mastectomy (RRM) and immediate breast reconstruction (IBR):

Gahm J et al. (2013) reported on breast sensibility after bilateral risk-reducing mastectomy and immediate breast reconstruction (IBR) from a small prospective study of 46 patients. The primary aim of this study was to prospectively compare breast sensibility before and after RRM in a consecutive series of women. The study also investigated whether the nipples were less numb if the nipple areola complexes (NACs) were spared compared with regrafted nipple tips. Forty-six women who selected bilateral RRM with immediate reconstruction using implants at the Karolinska University Hospital, Solna, Stockholm, Sweden, were included in the study. The median patient age at the time of surgery was 39 years (range 26-58). All patients were evaluated preoperatively and at least 2 years postoperatively (median 29 months). Tactile, thermal and nociceptive cutaneous sensibilities were studied with quantitative techniques. The patients at the postoperative evaluation completed a questionnaire about subjective feelings in both breasts. The results showed that breast sensibility is significantly impaired after RRM. Additionally, the ability to experience sexual sensations in the breast is often lost. An NAC-sparing surgery did not result in better nipple sensibility.

Link to Timing of reconstruction - immediate versus delayed reconstruction:

Nelson JA et al. (2013) reported in a retrospective cohort study of all free autologous breast reconstruction patients between 2005 and 2009, focussing on ethnicity, cancer stage, unilateral or bilateral reconstructions, initial management, distance from the institution, and average income. Delayed reconstructions were compared to immediate reconstructions. All delayed reconstructions were surveyed to examine treatment and reconstruction decisions and satisfaction. Of 709 patients, 169 (24%) underwent delayed treatment. Delayed reconstruction patients had higher cancer stages ($p < 0.001$), higher rates of pre-reconstruction radiation therapy (64% vs. 20%, $p < 0.0001$) and higher rates of unilateral reconstruction (64% vs. 48%, $p < 0.001$). Seventy delayed patients responded to the survey (41%), with 75% having had initial mastectomy at an outside health system. Only 51% discussed immediate reconstruction prior to electing delayed treatment and 41% had no discussion regarding advantages or disadvantages to reconstructive options. Approximately

30% noted no choice in their reconstructive timing. Forty five percent would elect immediate reconstruction if given the option. The authors draw the conclusion from this study that women may not be receiving all available information prior to undergoing mastectomy for initial breast cancer treatment. As a significant portion of women electing delayed reconstruction would elect immediate reconstruction.

References:

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Jonas A. Nelson, John P. Fischer , M. Anne Radecki , Christina Pasick , Jennifer McGrath , Joseph M. Serletti , Liza C. Wu; Delayed autologous breast reconstruction: Factors which influence patient decision making. Journal of Plastic, Reconstructive & Aesthetic Surgery (2013) 66, 1513e1520

DIEP-Flap I (24/34)

Further information and references:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

Spiegel AJ, Khan FN. An intraoperative algorithm for use of the SIEA flap for breast reconstruction. Plast Reconstr Surg. 2007 Nov;120(6):1450-9: report on 99 SIEA flaps in a 3 ½ - period. Total flap loss: 5%. Overall fat necrosis and partial flap loss: 6.1%. No hernias.

DIEP-Flap II (25/34)

Further information:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

References:

Spiegel AJ, Khan FN. An intraoperative algorithm for use of the SIEA flap for breast reconstruction. Plast Reconstr Surg. 2007 Nov;120(6):1450-9: report on 99 SIEA flaps in a 3 ½ - period. Total flap loss: 5%. Overall fat necrosis and partial flap loss: 6.1%. No hernias.

Schaverien MV et al. Comparison of outcomes and donor-site morbidity in unilateral free TRAM versus DIEP flap breast reconstruction. J Plast Reconstr Aesthet Surg. 2007;60(11):1219-24: No significant difference in postoperative outcomes or in the subjective ability to perform activities of daily living.

Results of Bonde CT et al. Abdominal strength after breast reconstruction using a free abdominal flap. J Plast Reconstr Aesthet Surg. 2007;60(5):519-523 are accordingly except for eccentric muscle strength pt. with a DIEP had a small ,but sign. advantage over pts with MS-2 TRAM.

Chen CM. Et al. Immediate postoperative complications in DIEP versus free/muscle-sparing TRAM flaps. Plast Reconstr Surg. 2007 Nov;120(6):1477-82: results of 200 consecutive cases of both techniques showed no differences concerning complications.

DIEP-Flap III (26/34)

Further information and references:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

Chen CM. Et al. Immediate postoperative complications in DIEP versus free/muscle-sparing TRAM flaps. Plast Reconstr Surg. 2007 Nov;120(6):1477-82: results of 200 consecutive cases of both techniques showed no differences concerning complications.

Spiegel AJ, Khan FN. An intraoperative algorithm for use of the SIEA flap for breast reconstruction. Plast Reconstr Surg. 2007 Nov;120(6):1450-9: report on 99 SIEA flaps in a 3 ½ - period. Total flap loss: 5%. Overall fat necrosis and partial flap loss: 6.1%. No hernias.

Schaverien MV et al. Comparison of outcomes and donor-site morbidity in unilateral free TRAM versus DIEP flap breast reconstruction. J Plast Reconstr Aesthet Surg. 2007;60(11):1219-24: No significant difference in postoperative outcomes or in the subjective ability to perform activities of daily living.

Results of Bonde CT et al. Abdominal strength after breast reconstruction using a free abdominal flap. J Plast Reconstr Aesthet Surg. 2007;60(5):519-523 are accordingly except for eccentric muscle strength pt. with a DIEP had a small ,but sign. advantage over pts with MS-2 TRAM.

Pedicled/ Free TRAM I (27/34)

No further information

References:

Simon AM et al. Comparison of unpedicled and bipedicled TRAM flap reconstructions: assessment of physical function and patient satisfaction. PRS 2004 Jan; 113(1):136-40

Spear SL et al. Effect of obesity on flap and donor-site complications in pedicled TRAM flap breast reconstruction. Plast Reconstr Surg. 2007 Mar;119(3):988-95: Obese patients (BMI ≥ 30) have in contrast to normal weight or overweight pts. (BMI up to 29) a significantly higher risk for developing overall and multiple flap complications.

Elliott LF et al. The 3-hour muscle-sparing free TRAM flap: safe and effective treatment review off 111 consecutive free TRAM flaps in a private practice setting. Plast Reconstr Surg. 2007 Jul;120(1):27-34.

Pedicled/ Free TRAM II (28/34)

No further information

References:

Simon AM et al. Comparison of unpedicled and bipedicled TRAM flap reconstructions: assessment of physical function and patient satisfaction. PRS 2004 Jan; 113(1):136-40

Spear SL et al. Effect of obesity on flap and donor-site complications in pedicled TRAM flap breast reconstruction. Plast Reconstr Surg. 2007 Mar;119(3):988-95: Obese patients (BMI ≥ 30) have in contrast to normal weight or overweight pts. (BMI up to 29) a significantly higher risk for developing overall and multiple flap complications.

Elliott LF et al. The 3-hour muscle-sparing free TRAM flap: safe and effective treatment review off 111 consecutive free TRAM flaps in a private practice setting. Plast Reconstr Surg. 2007 Jul;120(1):27-34.

Radiotherapy after Autologous Reconstruction I (29/34)

Further information:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

References:

Spiegel AJ, Khan FN. An intraoperative algorithm for use of the SIEA flap for breast reconstruction. Plast Reconstr Surg. 2007 Nov;120(6):1450-9: report on 99 SIEA flaps in a 3 ½ - period. Total flap loss: 5%. Overall fat necrosis and partial flap loss: 6.1%. No hernias.

Radiotherapy after Autologous Reconstruction I (30/34)

Further information:

A further method to preserve muscular strength of the abdominal wall is the SIEA flap based on the superficial inferior epigastric artery. This free flap can be performed only when the size of the SIEA is 1.5 mm in diameter or wider. This method has a rather high rate of postoperative vascular revisional surgery.

References:

Spiegel AJ, Khan FN. An intraoperative algorithm for use of the SIEA flap for breast reconstruction. Plast Reconstr Surg. 2007 Nov;120(6):1450-9: report on 99 SIEA flaps in a 3 ½ - period. Total flap loss: 5%. Overall fat necrosis and partial flap loss: 6.1%. No hernias.

Algorithm of Breast Reconstruction (31/34)

No further information

No references

Algorithm of Autologous Breast Reconstruction (1) (32/34)

No further information

No references

Algorithm of Autologous Breast Reconstruction (2) (33/34)

No further information

No references

Algorithm of Implant Breast Reconstruction (34/34)

Further information

Link to pre-mastectomy sentinel node biopsy:

The pre-mastectomy sentinel lymph node biopsy (PM-SLNB) is a technique that provides knowledge regarding nodal status prior to mastectomy. Because radiation exposure is associated with poor outcomes in breast reconstruction and reconstructed breasts can interfere with the planning and delivery of radiation therapy (RT), information regarding nodal status has important implications for patients who desire immediate breast reconstruction. This study explores the safety and utility of PM-SLNB as part of the treatment strategy for breast cancer patients desiring immediate reconstruction. Teven et al. [2013] reviewed the charts of adult patients (≥ 18 years old) who underwent PM-SLNB from January 2004 to January 2011. PM-SLNB was offered to patients with stage I or IIa, clinically and/or radiographically node-negative breast cancer who desired immediate breast reconstruction following mastectomy. PM-SLNB was also offered to patients with ductal carcinoma in situ if features concerning for invasive carcinoma were present. Ninety-one patients underwent PM-SLNB of 94 axillae. PM-SLNB was positive in 25.5% of breasts ($n = 24$). Nineteen node-positive patients (79.2%) have undergone or planning to undergo delayed reconstruction at our institution. Seventeen of these 19 node-positive patients (89.5%) have received adjuvant RT. Two patients (10.5%) elected against RT despite our recommendation for it. No biopsy-positive patient underwent immediate reconstruction or suffered a radiation-induced complication with their breast reconstruction. There were two minor complications associated with PM-SLNB, both in node-negative patients. This study demonstrates the utility of PM-SLNB in providing information regarding nodal status, and therefore the need for adjuvant RT, prior to mastectomy. This knowledge can be used to appropriately counsel patients regarding optimal timing of breast reconstruction.

References

Teven C, Agarwal S, Jaskowiak N, Park JE, Chhablani A, Seitz IA, Song DH. Pre-mastectomy sentinel lymph node biopsy: a strategy to enhance outcomes in immediate breast reconstruction. *Breast J.* 2013 Sep-Oct;19(5):496-503. doi: 10.1111/tbj.12151. Epub 2013 Jun 17.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Adjuvant Endocrine Therapy

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➤ Versions 2002–2013:

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Friedrichs / Gerber / Göring / Harbeck /
Huober / Jackisch / Lisboa / Maass /
Möbus / Müller / Oberhoff / Schaller /
Scharl / Schneeweiss / Schütz /
Solomeyer / Stickeler / Thomssen /
Untch / von Minckwitz**

➤ Version 2014: **Jackisch / Lück**

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Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1

GR: A

AGO: ++

Endocrine responsiveness:

Immunohistochemistry (ER and / or PgR)

0% pos. cells: endocrine non-responsive

≥ 1 pos. cells: endocrine responsive

Status unknown: endocrine responsive

Adjuvant Endocrine Therapy

Assessment of Menopausal Status

Oxford / AGO
LoE / GR

Assessment of menopausal status

- Menstruation history +
- FSH, E2 ++

Assessment of ovarian reserve

- Anti-Müllerian Factor 3b B +/-
- Antral follicle count 3b B +/-

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Adjuvant Endocrine Therapy in Premenopausal Patients

Oxford / AGO
LoE / GR

Standard therapy in endocrine responsive tumors:

- **Endocrine therapy** **1a A ++**
- **Chemo-endocrine therapy** **1a A ++**
(dependent on individual risk
and level of ER/PgR expression)

Adjuvant Endocrine Therapy in Postmenopausal Patients

Oxford / AGO
LoE / GR

➤ **Endocrine responsive & doubtful:
Endocrine therapy**

1a A ++

➤ **Endocrine therapy
sequentially after CT**

2b C ++

➤ **Non-responsive:
No endocrine therapy**

1a A ++

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General Principles in Adjuvant Endocrine Therapy

AGO ++

- **Treatment duration might be considered up to 10 years, up to 10 years based on the individual risk of relapse (e.g., N+ status at presentation)**
 - **Premenopausal: after 5 yrs. of Tam; EAT: 5 yrs. of TAM**
 - **Postmenopausal: after 5 yrs. of Tam: EAT 5 yrs. Tam or AI**
- **Duration, choice & sequence of AI or Tam mainly rely on menopausal status and side effects**
- **Switch to another endocrine treatment (Tam or AI) is better than to stop**
- **AI as first treatment preferably in patients at high risk (lobular cancers)**
- **So far no evidence for AI > 5 yrs**

Duration of Adjuvant Endocrine Treatment in Premenopausal Patients

Oxford / AGO
LoE / GR

| | | | | |
|---|----------------------|----|---|-----|
| Tamoxifen* | 5 yrs. (vs. shorter) | 1a | A | ++ |
| Tamoxifen* | 10 yrs.(vs. 5 yrs) | 1b | A | ++ |
| GnRH-analogues** | 2–5 yrs. | 1b | A | ++ |
| Induction of amenorrhea after CT by GnRH-analogues | | 2b | D | +/- |

* Treat as long as tolerable and premenopausal **LoE 2b**

**The prognosis of the disease after GnRHa (≥ 2 years) treatment is independent of ovarian function (restored / non restored)

Adjuvant (Chemo-)endocrine Therapy in Premenopausal Patients

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➤ High or intermediate risk

➤ Chemo → Tam

1a A ++

➤ Chemo → Tam + GnRHa

1a B +/-

➤ < 40 yrs.

3a C -

➤ Low or intermediate risk

➤ Tam alone

1a A ++

➤ Tam + GnRHa

1a B +

➤ GnRHa alone

1a B +

(only if relevant contraindications for Tam)

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Adjuvant Endocrine Therapy with Aromatase-Inhibitors in Premenopausal Patients

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| | Oxford / AGO LoE / GR | |
|--|--------------------------|------------|
| ➤ GnRHa + AI | 1b B | - |
| ➤ If severe contraindications against Tam | 5 D | +/- |
| ➤ AI alone | 1c A | -- |
| ➤ AI after GnRHa (induced amenorrhea) | 5 D | -- |
| ➤ Upfront AI in patients with chemotherapy-induced amenorrhea (CIA, TIA) | 4 C | -- |
| ➤ EAT in perimenopausal pts. with validated postmenopausal status after 5 yrs. of Tam | 2b B | + |

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

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CT + GnRHa

(GnRHa application > 2 weeks prior to chemotherapy)

➤ HR-

➤ HR+

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1b B -

1b B -

1b B -

Impairment of CT – effect cannot be excluded!

Fertility preservation counselling*

4 C +

Fertility preservation with

assisted reproduction therapy

4 C +

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Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer

| | Oxford / AGO LoE / GR | | |
|---|--------------------------|---|-----|
| ➤ Barrier methods | 5 | D | + |
| ➤ Sterilization (tubal ligation / vasectomy) | 5 | D | + |
| ➤ Non-hormonal intrauterine devices (IUDs) | 5 | D | + |
| ➤ Levonorgestrel-releasing IUDs | 5 | D | - |
| ➤ Removal in newly diagnosed patients | 4 | D | +/- |
| ➤ Timing methods | 5 | D | - |
| ➤ Injectable progestin-only contraceptives | 5 | D | - |
| ➤ Progestin-only oral contraceptives | 5 | D | - |
| ➤ Combined oral contraceptives | 5 | D | - |

No trial included women after diagnosis of breast cancer, non-estrogen containing devices do not increase the risk to develop primary breast cancer

Adjuvant Tamoxifen / Aromatase Inhibitors (AI) Treatment in Postmenopausal Patients

Oxford / AGO LoE / GR

- **AI for 5 yrs.**
 - Preference in lobular inv. cancers
- **Sequential therapy for 5 yrs.**
 - Tam followed by AI
 - AI* followed by Tam
- **Tamoxifen 20 mg/d for 5-10 yrs.**

| | | |
|----|---|----|
| 1a | A | + |
| 2b | B | + |
| | | ++ |
| 1a | A | |
| 1b | C | |
| | | |
| 1a | A | ++ |

Preference in N+

*Currently data available for letrozole, only

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Endocrine Therapy after Tamoxifen in postmenopausal patients

**Oxford / AGO
LoE / GR**

After 5 yrs. tamoxifen (EAT)

- **AI up to 3 to 5 yrs.**
 - **Node-positive disease**
 - **Long tamoxifen-free interval**

**Consider EAT with AI for pts. who changed
to postmenopausal status during 5 yrs. Tam**

| | | |
|-----------|----------|-----------|
| 1b | A | ++ |
| 2b | B | ++ |
| 2b | B | + |

- **Continuation of Tam up to total 10 yrs.**

| | | |
|-----------|----------|-----------|
| 1a | A | ++ |
|-----------|----------|-----------|

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Ovarian Function Preservation – Comparison of Randomized Trials

| | ZORO | PROMISE | Munster et al. - US |
|--|--|--|---|
| Patient number | 60 (60 HR-) | 281 (50 HR-) | 49 (13 HR-) of 124 |
| Age median | 38 years | 39 years | 39 years |
| Treatment | goserelin | triptorelin | triptorelin |
| Start of treatment | >2 weeks prior to cht | >1 week prior to cht | > 1 week prior to cht |
| Primary Endpoint | menstruation at month 6 after chemotherapy | rate of early menopause at month 12 after chemotherapy | menstruation rate within 2 years after cht |
| Primary objective | to detect 30% absolute increase of menstruation rate | to detect at least 20% absolute reduction in early menopause | to detect 20% difference in amenorrhea rate - from 10% to 30% |
| Multivariable analysis | age as only independent predictive factor | treatment as only independent predictive factor | n.d. |
| Resumption of menses at month 12 in HR- cohort | 83% with LHRH vs. 80% w/o | 93% with LHRHa vs. 74% w/o | 74% with LHRH vs. 68% w/o |
| Median time to restoration of menstruation (months) | 6.1 with LHRHa vs. 6.8 w/o; p=0.30 | not reached with LHRH vs. 6.7 w/o; p=0.07 | 5.8 with LHRH vs. 5.0 w/o; p=0.58 |
| Cyclophosphamide dose | 4600 vs. 4700mg | 4080 vs. 4008 mg | n.r. |

Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Metaanalysis of Individual Patient Data from Randomised Adjuvant Trials

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| Chemo ± LHRH | n | RRR* | 95% CI | |
|---------------------|----------|-------------|------------------|----------|
| Age ≤ 40 years | 714 | -24.7 | (-39.5 to 6.2), | p = 0.01 |
| Age > 40 years | 1662 | - 5.1 | (-20.1 to 12.7), | p = 0.55 |

Chemo + Tam ± LHRH

| | | | | |
|----------------|-----|-------|------------------|----------|
| Age ≤ 40 years | 81 | -31.2 | (-67.5 to 46.0), | p = 0.33 |
| Age > 40 years | 284 | 5.3 | (-33.3 to 66.3), | p = 0.82 |

(Chemo ± Tam) ± LHRH (combination of previous comparisons: chemo ± LHRH and chemo + Tam ± LHRH!)

| | | | | |
|----------------|-----|-------|------------------|----------|
| Age ≤ 40 years | 795 | -25.2 | (-39.4 to -7.7), | p = 0.01 |
| Age > 40 years | 284 | - 3.9 | (-18.1 to 12.9), | p = 0.63 |

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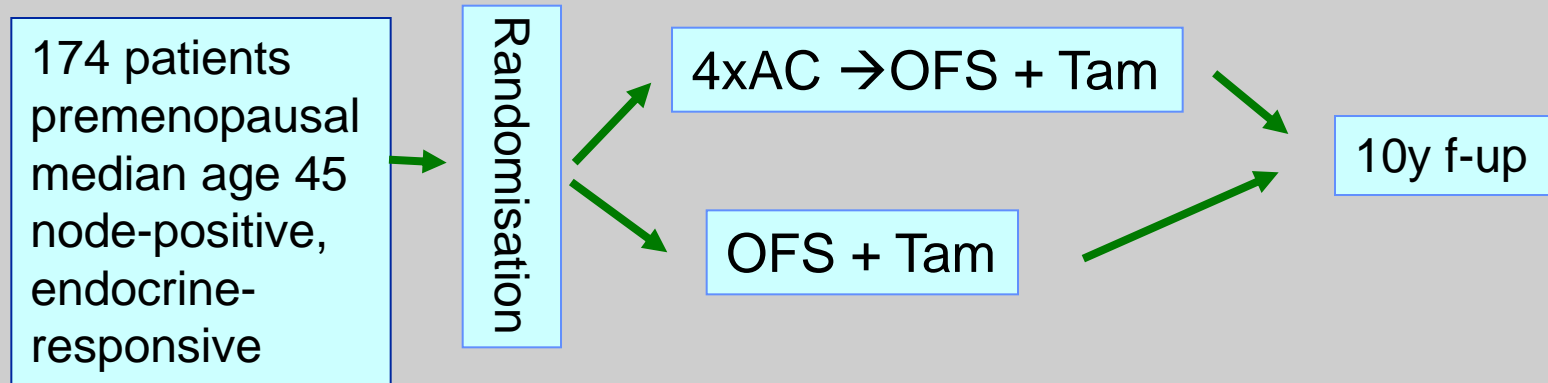
References

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* relative risk reduction

Cuzick J et al., Lancet 2007; 369:1711-23

Chemo + Castration + Tam vs. Castration + Tam



DFS hazard ratio = 1.02 (0.57-1.83); P = 0.94
OS hazard ratio = 0.97 (0.44-2.16); P = 0.94

- Trial was closed prematurely due to low accrual rate.
- No evidence that AC chemotherapy provides additional disease control for premenopausal patients with lower-risk node-positive endocrine-responsive breast cancer who receive adequate adjuvant endocrine therapy.

GnRH-a: RCTs

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| | Badawy (2009) | | Ismail-Khan (2008) | | ZOR0 (2009) | |
|--------------------------|-------------------------------------|------------|--------------------------|-------------|--------------------------|---------------|
| | Chemo+ GnRH-a | Chemo | Chemo+ GnRH-a | Chemo | Chemo+ GnRH-a | Chemo |
| N | 39 | 39 | 25 | 24 | 30 | 30 |
| Pts.-character. | | | | | | |
| pT | - | - | - | - | 1–4 | 1–4 |
| N+ | - | - | 50 % | 50 % | 35% | 42% |
| Horm. rec. pos. | - | - | - | - | 0% | 0% |
| Age (med., years) | 30 | 29 | 39 | 39 | 35 | 38 |
| Med. F/U [mths] | 8 | 8 | 18 | 18 | 24 | 24 |
| GnRH-a appl. | during Chemo | | during Chemo | | during Chemo | |
| Chemotherapy | 6x FA₅₀₀C d1q6-8w | | 6x FAC, AC-T, TAC | | 6x FEC, AC-T, TAC | |
| Regular menstr. | | | | | | |
| ≤1 year | 90% | 33% | 83% | 79% | 83% | 80% |
| - end of F/U | - | - | 88% | 84% | 93% | 97% |
| Pregn. / Births | - | - | 0 | 8% | 3% / 3% | 3% / 0 |

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GnRHa: Observation Studies

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| | Recchia 2006 | Fox 2003 | Del Mastro 2006 | Urrutico- echea 2008 |
|--|--|---------------------------------------|--|-------------------------------------|
| N | 100 | 24 | 29 | 60 |
| Pts.-character. | | | | |
| pT | 2–3 | 1–2 | 1–3 | - |
| N+ | 58% | 50% | 55% | - |
| Horm. rec. pos. | 52% | - | 86% | 72% |
| Age (med., years) | 43 | 35 | 38 | 34 |
| Med. F/U [mths] | 75 | 34 | 72 | 43 |
| GnRH-a application | during Chemo up to 1 year | during Chemo | | |
| Chemotherapy | FAC, CMF, E₁₂₀- CMF, Taxane, high-dose Chemo | AC, AC-T, FAC, AT- CMF | FEC, AC-T | FEC, FEC-T, AC, EC-T |
| Regular menstr. ≤1 year after Chemo | 100% (<40 y.) 56% (>40 y.) | 96% - | 94% (<40y) 42% (>40y) | 86% - |
| Pregnancies/ Births | 3% / 2% | 21% / 8% | - | 20% / 16% |

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Trials with Aromatase Inhibitors

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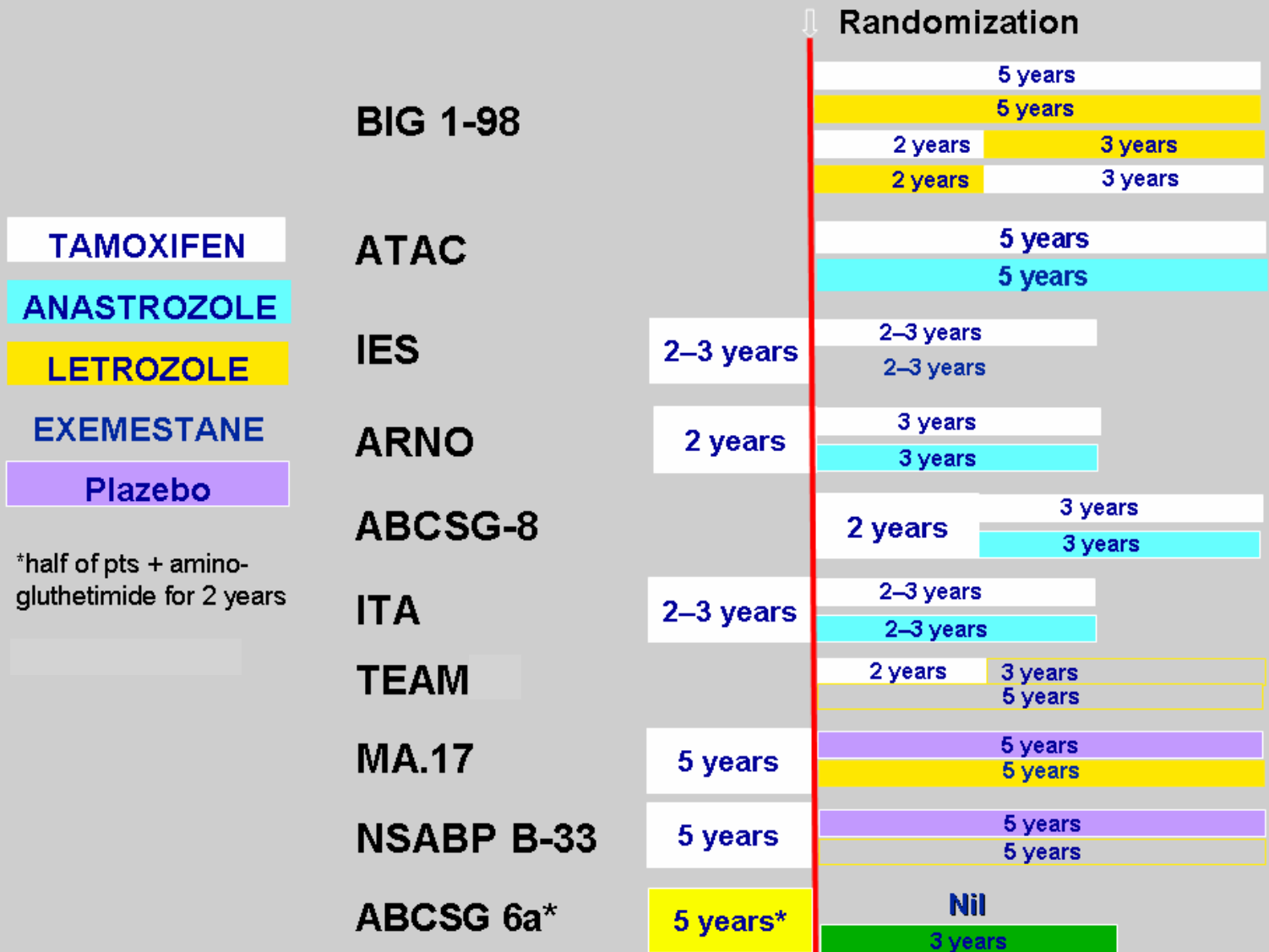
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Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Upfront and Extended Therapy

| Trial | Source | AI | Indication | Pts | F/U mo | DFS/BCFS/TTR/TTDR/CBC | OS | Side Effects | Remarks |
|-----------------|-----------------------------------|----|----------------------------|------|--------|---|-----------------------|--|---|
| ATAC | ATAC Trialists' Group 2010 | A | upfront vs T | 6241 | 120 | HR + patients: DFS HR 0.86, p=0.003 TTR 0.79, p=0.0002 TTDR 0.85, p=0.02 | HR 0.87 p=0.4 | SAE T>A gyn AE T>A VE T>A SE A>T | only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL → (Cella 2006) |
| BIG 1-98 | BIG 1-98 Collaborative Group 2011 | L | upfront ² vs T | 4922 | 97 | DFS = 0.86 P = 0,007 | P = 0,048 | SAE T=L gyn AE T>L TE T>L CE L>T SE L>T | L>T in particular in case of N+ |
| NCIC CTG MA.27 | Goss 2010 | E | upfront vs A | 7576 | 49 | EFS HR 1.02 DDFS HR 0.95 | ns | Osteoporosis A>E El. liver enzymes E>A Hyperlipidaemia A>E | Randomization for Celecoxib cancelled |
| Extended | Adjuvant | | Therapy | | | | | | |
| MA 17 | Goss 2005 | L | extended after 5y T vs P | 5170 | 30 | DFS HR 0.58, p<0.01 TTDR HR 0.60, p<0.01 CBC HR 0.63, p=0.13 | HR 0,61 in N+, p=0,04 | CE L=P SE L>P | QoL ↓ (Whelan 2005) Lipids → (Wasan 2005) |
| ABSCG6a | Jakesz 2007 | A | extended after 5y T vs Nil | 856 | 62 | DFS HR 0.642 p=0.031 | ns | | |
| NSABP-B33 | Mamounas 2008 | E | Extended after 5y T Vs P | 1598 | 30 | DFS HR 0,68 p=0,07 RFS HR 0,44 p= 0,004 | ns | SE E=P after 6 Mo | Grad 3 AE E>P 9%vs3%, p=0,03 Profit from E particular in N+ |

A anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; SAE, serious adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. * only HR positive population

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Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Switching/Sequential trials

| Trial | Source | AI | Indication | Pts | F/U mo | DFS/BCFS/TTR/ TTDR/CBC | OS | Side Effects | Remarks |
|---------------------------|----------------------|----|---|--------------|-----------|---|---|---|--|
| IES | Bliss JM | E | switch after 2-3y T vs T | 4599 | 91 | DFS HR 0.76, ITT p<0.01 DFS HR 0.75, ER+/u BCFS HR 0.76, ITT, s BCFS HR 0.75, ER+/u TTDR HR 0.83, ITT, s TTDR HR 0.82 ER+/u, s | HR, 0.86; 95% CI, 0.75 to 0.99; P = .04). | gyn AE T>A TE T>E SE E>T diarrhea E>T | Random after 2-3y T, only pts. relapse-free after 2-3 y T were included |
| ITA | Boccardo 2006 | A | switch after 2-3y T vs T | 448 | 64 | EFS HR 0.57, p<0.01 RFS HR 0.56, p=0.01 | ns | SAE T>A | Random after 2-3y T, only pts. relapse-free after 2-3 y T were included |
| ABCSG - 08 ARNO95 | Jakesz 2005 | A | switch after 2y T vs T | 3224 | 28 | DFS HR 0.59, p<0.01 TTR HR 0.60, p<0.01 TTDR HR 0.61, p<0.01 | ns | TE T>A SE A>T | |
| ABCSG -08 | Jakesz 2005 | A | switch after 2y T vs T | 2529 | 31 | DFS HR 0.61, p=0.01 TTDR HR 0.68, p=0.11 CBC HR 0.45, p=0.07 | ns | TE T>A SE A>T | Analysis of switch data only, random upfront |
| ARNO 95 | Kaufmann 2007 | A | switch after 2y T vs T | 979 | 30 | DFS HR 0.66, p=0.049 | HR 0.53, p=0.045 | SAE T>A 30,8 vs 22,7 % | No chemotherapy, random after 2 y T; only pts relapse-free after 2 y T were included |
| BIG 1-98 | Regan et al 2011 | L | switch after 2y T vs. Let switch after 2y L vs. Let. | 1548 1540 | 97 | disease-free survival; 87.5%, 87.7%, 85.9% ns | 89.9%, 88.7%, 88.1% ns | SE L>T VE L = T | Comparison of switch L/T or T/L vs. L |
| TEAM | Van de Velde 2011 | E | TEAM: E alone vs Tam switch after 2 – 3 y to E | 4868 4898 | 60 | hazard ratio 0.97, 95% CI 0.88-1.08; p=0.60) | n.a. | DVT; endometrial > switch Musculoskeleta l problems hyperlipidaemi a > E mono | |
| N-SAS BC03 | Aus Japan 2010 | A | Tam 5 y vs Tam→ A switch after 1 – 4 y Tam | 706 | 42 | DFS: 0.69 P = 0.14 RFS 0.54 P = 0.06 | n.a. | dito | |
| Meta- analysis | | | | | | | | | |
| ARNO95 ABCSG8 ITA | Jonat 2006 | A | switch (2-3y T) | 4006 | | DFS HR 0.59, p<0.01 | HR 0.71, p=0.04 | | with heterogeneity |

A, anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; Cx, chemotherapy; DFS, disease-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; ITT, intent to treat; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; s, significant; serious adverse event; SE, skeletal event; T tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; u, unknown; VE, vascular event; (?) according to retrospective analysis.

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Further
Information

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/22)

No further information

No references

Assessment of Steroid Hormone Receptor Status (3/22)

Further information and references:

Endocrine responsiveness can be predicted by analysis of hormone receptor status and is positively correlated to the degree of receptor expression in tumor tissue (1, 2, 3). The assessment should be performed in a well-established, skilled laboratory. Immunohistochemical assays appear to be superior in predicting response to adjuvant endocrine therapy compared to standard ligand-binding assays (3). Since the risk-benefit ratio of endocrine therapy is excellent and the majority of tumors is endocrine responsive, endocrine therapy is suggested if receptor status is unknown and no tumor tissue is available for testing.

Statement 1 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis))

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Adjuvant Endocrine Therapy Assessment of Menopausal Status (4/22)

Further information:

The menstruation history is reliable only in women < 45 years of age. A more precise evaluation, especially in perimenopausal patients is possible with the measurement of FSH and E2 levels in peripheral blood. Hormonal replacement should be stopped at least 6 weeks before measurement. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression [1, 2]. Low AMH (antimüllerian hormone) levels seem to be indicative for reduced ovarian reserve and chemotherapy-related amenorrhea (CRA) in chemotherapy-treated breast cancer patients [3, 4, 5, 6]. Antral follicle count, defined as the sum of follicle diameters of all follicles of 10mm in both ovaries. [7]

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Adjuvant Endocrine Therapy in Premenopausal Patients (5/22)

Further information:

The EBCTCG performed a meta-analysis of randomized trials evaluating the effect of systemic hormone and cytotoxic treatment of early breast cancer. Results after 15-year follow-up were published in 2005: Adjuvant polychemotherapy in women younger than 50 years resulted in a 10% absolute gain in 15-year survival (HR 42% vs. 32%). The absolute improvement in survival was twice as great at 15 years as it was at 5 years (10% vs. 4.7%). The reduction in risk of recurrence was similar in the presence or absence of tamoxifen (1). The benefit of tamoxifen was restricted to women with ER-positive or ER-unknown breast cancer. The 15-year absolute improvements in relapse and mortality associated with 5 years tamoxifen were 12% and 9%, respectively (1). 5 years of use reduced the annual breast cancer death rate by 31%, largely irrespective of age (<50 years, 50 to 69 years, ≥ 70 years), and of the use of chemotherapy (1). The benefit from 5 years of tamoxifen in women younger than 50 years was similar to that obtained by older women. The proportional reductions in both recurrence and mortality were irrespective of nodal status, but the absolute improvement in survival was greater in nodal positive disease (1). Similar results were found in the International Breast Cancer Study Group-1393 trial (2). 5 years of tamoxifen after adjuvant chemotherapy resulted in improvement of DFS (hazard ratio [HR] for tamoxifen v no tamoxifen 0.59; 95% CI, 0.46 to 0.75; P .0001). However, this was seen in the ER-positive cohort only. Tamoxifen had a detrimental effect on patients with ER-absent tumors compared with no tamoxifen in an unplanned exploratory analysis (HR 2.10; 95% CI, 1.03 to 4.29; P .04). Patients with ER-positive tumors who achieved chemotherapy-induced amenorrhea had a significantly improved outcome (HR for amenorrhea v no amenorrhea 0.61; 95% CI, 0.44 to 0.86; P .004).

The benefit from chemotherapy is dependent on the risk for relapse and metastasis and might be low even in a lower risk node positive endocrine responsive situation (3)

References:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365 (9472): 1687-717, 2005.
2. Colleoni M et al.: Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group Trial 13-93. *J Clin Oncol* 24 (9): 1332-41, 2006.
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Statement 1 (LoE 1a: ref. 1 (consistent prospective RCT and metaanalysis)

Statement 2 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis)

Statement 3 (LoE 1b; ref. 3 prospective RCT with narrow confidence interval)

Adjuvant Endocrine Therapy in Postmenopausal Patients (6/22)

Further information:

Endocrine therapy is one important systemic therapy option in primary breast cancer. The last Oxford Overview Analysis estimates an at least 31% relative reduction of mortality by adjuvant endocrine therapy (EBCTCG 2005). Endocrine therapy is only effective in steroid hormone receptor positive tumors, but not in steroid hormone receptor negative tumors (EBCTCG 2005, Hutchins 1999).

These data result in the following therapy recommendations: Patients with receptor negative tumors (ER– and PgR–) should not receive endocrine therapy (neither tamoxifen nor aromatase inhibitors in postmenopausal patients; also not ovarian ablation in premenopausal patients). An overall survival benefit by prevention of contralateral breast cancer has not been shown (Hutchins 1999). Patients with receptor positive tumors (either ER+ or PgR+) should receive endocrine therapy. An exception to this principle may only be discussed in individual patients with a very low relapse risk (e.g. node negative low-risk according to St. Gallen 2005). If chemo-endocrine therapy is indicated, tamoxifen should be given sequentially after adjuvant chemotherapy. Tamoxifen given concomitantly with adjuvant chemotherapy seems to be less effective regarding DFS and OS than tamoxifen given sequentially. Thus, simultaneous endocrine therapy may decrease chemotherapy effectiveness. However, clinical data for this statement are only available for tamoxifen, but not for other endocrine therapies (Albain 2002). The indication for chemo-endocrine therapy should depend on the individual relapse risk: In patients with receptor-positive tumors and increased risk for relapse (e.g. node positive tumors; node negative tumors with G3, elevated tumor levels of uPA/PAI-1 or very young patients), additional adjuvant chemotherapy does improve patient outcome (EBCTCG 1998, Fisher 2001, Jänicke JNCI 2001).

References:

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General Principles of Adjuvant Endocrine Therapy AGO ++ (7/22)

Further information:

More and more evidence is arising that hormone-receptor positive tumors have to be treated as long as possible, potentially life-long with endocrine therapy. As current trials report only on a maximum duration of 10 years, the commission is currently restricting its recommendation to this duration. However, it is likely that a patients starting endocrine treatment today will be informed in 10 years time that even longer treatment is of benefit as current trial are underway comparing 10 vs 15 years of treatment.

Given the small absolute differences observed for various approaches to give tamoxifen and/or aromatase-inhibitors, the commission felt that it is more important to motivate patients to comply at full dose the whole treatment period than to stick on one of these approaches. So to switch to another endocrine treatment is better than to stop or to loose compliance of the patient.

As tumor with high early relapse risk (e.g. node-positive disease) or as recently been shown in lobular invasive cancers, aromatase-inhibitors have shown their largest benefit compared to tamoxifen and should therefore be considered as first treatment approach.

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References of AI trials: see slide 21 and 22.

Duration of Adjuvant Endocrine Treatment in Premenopausal Patients (8/22)

Further information:

The EBCTCG meta-analysis as well as several large randomised trials addressed the optimal duration of tamoxifen use. According to the EBCTCG meta-analysis 5 years of tamoxifen are significantly advantageous over 1 to 2 years concerning the risk of recurrence (proportionate reduction 15.2%; $P < .001$) and mortality (proportionate reduction 7.9%; $P = .01$) after 15 years of follow-up [1]. The NSABP-B14 study [2] and the Scottish adjuvant tamoxifen trial [3] compared 5 years to 10 years of adjuvant tamoxifen for women with early-stage ER-positive node-negative and node positive breast cancer and did not find any advantage for a longer than 5 year duration of use, on the contrary, there was a trend toward a worse outcome associated with a longer duration of treatment. An ECOG trial [4] randomized patients after 5 years of tamoxifen to continuation versus cessation of treatment. Continued tamoxifen was associated with a longer time to relapse but with no difference in OS. Recently first results of the ATLAS-trial showed a slight, but significant reduction in the risk for relapse without a significant improvement of the risk for death with 10 compared to 5 years of tamoxifen use [4].

Therefore 5 years of adjuvant tamoxifen are recommended.

In most studies GnRH was given for 2-3 years. It has not been evaluated whether a longer duration is of advantage. Chemotherapy induced amenorrhoea (CIA) seems to be a good prognostic factor. A meta-analysis about the influence of CIA on the prognosis could prove a significant advantage of survival for amenorrhoeic patients in 15 of 23 included studies [5]. Newer data with modern type chemotherapy suggest similar outcome [6, 7]. So far there is no data to show that re-start of menses is a predictive factor to give GnRH [8, 9]. This is a question to be answered by ongoing studies.

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Adjuvant (Chemo-)endocrine Therapy in Premenopausal Patients (9/22)

Further information:

Tamoxifen is the endocrine standard treatment in hormone sensitive premenopausal breast cancer [1-3, 6, 7, 9]. Tamoxifen only can be considered in special cases (low or intermediate risk) or if the patient does not consent or tolerate additional chemotherapy or GnRH therapy.

Best data for endocrine therapy with tamoxifen is given by the meta-analysis from the early breast cancer trialists' collaborative group [1]. Results after 15-year follow-up were published in 2005: Adjuvant polychemotherapy in women younger than 50 years resulted in a 10% absolute gain in 15-year survival (HR 42% vs. 32%). The absolute improvement in survival was twice as great at 15 years as it was at 5 years (10% vs. 4.7%). The reduction in risk of recurrence was similar in the presence or absence of tamoxifen. The benefit of tamoxifen was restricted to women with ER-positive or ER-unknown breast cancer. The 15-year absolute improvements in relapse and mortality associated with 5 years tamoxifen were 12% and 9%, respectively (1). 5 years of use reduced the annual breast cancer death rate by 31%, largely irrespective of age (<50 years, 50 to 69 years, ≥70 years), and of the use of chemotherapy. The benefit from 5 years of tamoxifen in women younger than 50 years was similar to that obtained by older women. The proportional reductions in both recurrence and mortality were irrespective of nodal status, but the absolute improvement in survival was greater in nodal positive disease. Similar results were found in the International Breast Cancer Study Group-1393 trial [2]. 5 years of tamoxifen after adjuvant chemotherapy resulted in improvement of DFS (hazard ratio [HR] for tamoxifen vs. no tamoxifen 0.59; 95% CI, 0.46 to 0.75; P .0001). However, this effect was seen in the ER-positive cohort only. Tamoxifen had a detrimental effect on patients with ER-absent tumors compared with no tamoxifen in an unplanned exploratory analysis (HR 2.10; 95% CI, 1.03 to 4.29; P .04). Patients with ER-positive tumors who achieved chemotherapy-induced amenorrhea had a significantly improved outcome (HR for amenorrhea vs. no amenorrhea 0.61; 95% CI, 0.44 to 0.86; P .004). The benefit from chemotherapy is dependent on the risk for relapse and metastasis and might be low even in a lower risk node positive endocrine responsive situation [3].

As a consequence of these data, all (international) consensus statements recommended single agent tamoxifen as the current standard adjuvant endocrine therapy for premenopausal women with endocrine responsive tumors (often preceded by chemotherapy).

Although there are more and more data available concerning GnRH-analogues (GnRHa) the role of GnRHa remains under active investigation (see studies). If GnRH are recommended, they should be combined with tamoxifen. GnRH +/- Tamoxifen can be considered for certain subgroups (<40years, premenopausal E2 levels after chemotherapy). “Very“ young women with hormone sensitive tumors had a significantly worse prognosis than patients with hormone insensitive tumors (25 % vs. 47 % 10-year-disease free survival HR=1.49, p=.014), particularly those who did not achieve amenorrhea compared with those who experienced some cessation of menses ($23\% \pm 6\%$ vs. $38 \pm 3\%$; HR=1.67; 95% CI=1.19-2.34; p=.003) in various trials of the timing and duration of adjuvant therapy containing CMF [4]. The explanation for this effect is that younger women do not develop ovarian suppression following chemotherapy. A meta-analysis about the influence of CIA on the prognosis could prove a significant advantage of survival for amenorrhoeic patients in 15 of 23 included studies [5].

A recent meta-analysis [6] of 14 randomized trials that involved over 13 000 patients assessing the effect of GnRHa \pm Tamoxifen \pm Chemotherapy concluded in concordance with an older meta-analysis [7]:

(A) GnRHa *monotherapy*: results suggest that adjuvant GnRHa monotherapy is similar to older chemotherapy protocols (eg. CMF) in terms of recurrence-free and overall survival in ER+ patients. There are insufficient data to compare GnRHa monotherapy to tamoxifen alone, but available results suggest that these treatments are comparable in terms of recurrence-free survival.

(B) GnRHa + *anti-oestrogen therapy*: there are insufficient data to compare the combination of an GnRHa plus tamoxifen to tamoxifen alone. Results suggest that the GnRHa plus tamoxifen combination may be superior to an GnRHa alone or to chemotherapy alone, but the chemotherapy protocols tested are outdated. The data comparing GnRHa plus aromatase inhibitors to GnRHa plus tamoxifen are currently inconclusive.

(C) GnRHa + *chemotherapy*: there are insufficient data to compare the GnRHa + chemotherapy combination to an GnRHa alone, although results from a single study suggest comparable efficacy in ER+ patients. There is a trend

towards improved recurrence-free and overall survival in patients who received an GnRHa plus chemotherapy combination in comparison to chemotherapy alone.

(D) *chemotherapy + tamoxifen + GnRHa*: there are only 365 patients in this metaanalysis that were randomized to chemotherapy + tamoxifen with or without GnRHa, 81 of them were ≤ 40 years of age at diagnosis. These limited data do not provide reliable support for the use of GnRH analogues in this situation.

In cases of relevant contraindications against tamoxifen GnRHa alone is an option with nearly the same effectiveness than Tamoxifen alone (ZIPP-trial) [8]. Two years of goserelin treatment was as effective as 2 years of tamoxifen treatment 15 years after starting therapy. In women who did not take tamoxifen, there was a large benefit of goserelin treatment on survival and recurrence, and in women who did take tamoxifen, there was a marginal potential benefit on these outcomes when goserelin was added.

Statement 1 (LoE 1a: ref. 1 (consistent prospective RCT and metaanalysis))

Statement 2 (LoE 1a: ref. 1&2 (consistent prospective RCT and metaanalysis))

Statement 3 (LoE 1b; ref. 3 prospective RCT with narrow confidence interval)

References:

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG).: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365 (9472): 1687-717, 2005.
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Adjuvant Endocrine Therapy with Aromatase-Inhibitors in Premenopausal Patients (10/22)

Further information:

First analyses of a prospective randomized study comparing Zoladex + Tamoxifen versus Zoladex + Anastrozole for 3 years showed a non-significant disadvantage for AI regarding DFS and OS. Side effects were different and were composed of typical effects of TAM and AI: arthralgia, bone pain, and fever were significantly more frequent in the Anastrozole group, whereas uterine polyps and thrombosis were significantly more frequent with TAM [1]. Therefore GnRH+Anastrozole should not be considered as an alternative to Tam alone or GnRH + TAM. In patients with contraindications against TAM consider GnRH alone. Smaller phase II studies with letrozole and exemestane in this indication support these results [6]

AI alone in premenopausal patients even in pts. with chemotherapy induced amenorrhea and postmenopausal hormone levels may be induced resumption of ovarian function [2,3,5]. Therefore AI's alone are not indicated in premenopausal women.

Premenopausal women who started with TAM and became postmenopausal during treatment and were switched to Letrozole revealed a significant greater benefit regarding DFS (HR 0.25; 95 % CI: 0.12-0.51) compared to primary postmenopausal pts (HR 0.69; 95 % CI: 0.52-0.91). However the OAS was comparable. Otherwise premenopausal pts. With letrozole reported significant more side effects and lower quality of life [3].

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT) **(11/22)**

Further information:

Chemotherapy carries a risk of permanent ovarian failure [1, 2]. Ovarian protection is therefore discussed in patients who want to preserve fertility.

Four observational studies reported an ovarian protektiv effekt of GnRHa. All concluded, that GnRH-a prevent ovarian function. Chemotherapy ranged from CMF, anthracycline-based until high-dose chemotherapy regimens. Especially in patients younger than 40 years nearly 90 % of all pts reported resumption of ovarian function. In pts. older than 40 years reappearance of ovary function was reported in only 50, although the recieved an ovarian protection. It is also seen that the real number of pregnancies and moreover living births were very low [3-6].

Only one of three RCT investigating the ovarian protection by GnRHa during chemotherapy revealed a preventive effect of GnRHa. In a unicentric study from Egypt 78 patients ages 18 to 40 years were randomized to FAC-chemotherapy with or without Goserelin [7]. They reported a resumed menstruation rate of 89.6% in the Goserelin arm and 33.3% in the observation arm ($p < 0.001$). The reported ovulating rate amounted to 69.2% respectively 25.6% and was also significant different with $P < 0.001$. Astonishing were the doses (5-Fluorouracil 500mg/m², Doxorubicin 500 mg/m², Cyclophosphamide 500 mg/m²) and schedules (day 1 and repeated every 6-8 weeks) of chemotherapy application. In this study node positive patients were also included, in which taxanes are indicated. The german ZORO-study [8] included adequate and modern chemotherapy regimens including taxanes in 60 pts. with hormone insensitive tumors. The menstruation rate in the Goserelin and observation arm after 6 months amounted to 70.0 respectively 58.6% ($p = 0.4219$). After two years of follow up all evaluable patients of both arms reported resumed ovarian function. In the third randomized trial from Florida [9] with 49 patients and Triptorelin the menstruation resumed at 6, 12 and 18 months of chemotherapy in the respective groups (Triptorelin vs. control) as follow: 44% vs. 60%, 83% vs. 79% and 88% vs. 84%. The study by Munster et al. Has not finished recruitment. Only 49 out of 124 planned pts were randomised. However, the reuslts are in concordance with the ZORO study. Supporting the fact that the observed effect of LHRH is at its best small. [9]

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

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Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer (12/22)

No further information

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Adjuvant Tamoxifen / Aromatase Inhibitors (AI) Treatment in Postmenopausal Patients (13/22)

Further information:

Tamoxifen 20mg/d given for 5 yrs improves DFS and survival in hormone receptor-positive primary breast cancer (EBCTCG 2005) compared to placebo and 10 years improves DFS over 5 years (ATLAS). Aromatase inhibitors have shown improvements for DFS and metastases-free survival. Additionally improved survival has also been shown in the MA.17 study for extended adjuvant therapy with letrozole for node positive patients (Goss 2004) and in the ARNO and IES (ER+/unknown) studies for the switching strategy to an AI. After 2-3 years of tamoxifen switching to an AI resulted in superior survival compared to continuing tamoxifen (Coombes et al 2006, Kaufmann et al. 2006). Also a small meta-analysis (Jonat 2005) including 3 studies (ARNO, ABCSG8 and ITA) showed superior survival for the AI arms. Also in receptor-positive patients with tamoxifen contraindications or intolerance (e.g. venous thrombosis, endometrium carcinoma, etc.), adjuvant aromatase inhibitor therapy is recommended. Combination therapy of tamoxifen with aromatase inhibitors is not more effective than tamoxifen therapy alone (Baum 2002) and should therefore not be administered.

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References of AI trials: see slide 22 and 23.

Endocrine Therapy after Tamoxifen in postmenopausal patients (14/22)

Further information:

As extended adjuvant therapy after 5 years of tamoxifen therapy letrozole (vs. placebo) and anastrozole (vs. nil) are superior to no additional endocrine therapy with regard to DFS (Davies, 2012, Goss 2005, Jakesz 2005). In node-positive patients, extended adjuvant therapy with letrozole therapy resulted in a significant OS advantage (Goss 2005). The ATLAS study recently showed also a benefit for patients continuing tamoxifen for another 5 years after pretreatment with tamoxifen. The CI of the HR is overlapping with the one of extended adjuvant letrozol treatment, so that both options are considered feasible. Letrozole could be started up to 30 months after cessation of tamoxifen (Goss 2005). An intent to treat analysis of the NSABP-B33 study showed a trend towards better DFS and a significant better RFS in favour of extended adjuvant therapy with exemestane compared to placebo (Due to the results of the MA.17 study recruitment in the B33 study was stopped and unblinded October 2003. At this time 1598 of 3000 planned patients were enrolled.

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Ovarian Function Preservation – Comparison of Randomized Trials (15/22)

Further information and references:

This overview compares the different randomised trials comparing fertility preservation with GnRHanalogue without GnRHanalogue.

Gerber B, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, Fischer D, Sommer HL, Conrad B, Ortmann O, Fehm T, Rezai M, Mehta K, Loibl S; German Breast Group Investigators. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. J Clin Oncol. 2011 Jun 10;29(17):2334-41. Epub 2011 May 2

Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, Giordano M, Garrone O, Pronzato P, Bighin C, Levaggi A, Giraudi S, Cresti N, Magnolfi E, Scotto T, Vecchio C, Venturini M. JAMA. 2011 Jul 20;306(3):269-76.

Randomized Trial Using Gonadotropin-Releasing Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer. Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacevic M, Gross-King M, Xu P, Carter WB, Minton SE. J Clin Oncol. 2012 Jan 9. [Epub ahead of print]

Gonadotropin-releasing hormone analogue for premenopausal women with breast cancer.
Loibl S, Gerber B. JAMA. 2011 Oct 26;306(16):1760; author reply 1760-1.

The study by Munster et al. Has not finished recruitment. Only 49 out of 124 planned pts were randomised. However, the results are in concordance with the ZORO study. Supporting the fact that the observed effect of LHRH is at its best small.

Use of Luteinising-Hormone-Releasing Hormone Agonists as Adjuvant Treatment in Premenopausal Patients with Hormone-Receptor-Positive Breast Cancer: A Metaanalysis of Individual Patient Data from Randomised Adjuvant Trials (16/22)

No further information

No references

Chemo + Castration + Tam vs. Castration + Tam (17/22)

No further information

No references

GnRHa: RCTs (18/22)

Further information:

Only one of three RCT investigating the ovarian protection by GnRHa during chemotherapy revealed a preventive effect of GnRHa. In a unicentric study from Egypt 78 patients ages 18 to 40 years were randomized to FAC-chemotherapy with or without Goserelin [1]. They reported a resumed menstruation rate of 89.6% in the Goserelin arm and 33.3% in the observation arm ($p < 0.001$). The reported ovulating rate amounted to 69.2% respectively 25.6% and was also significant different with $P < 0.001$. Astonishing were the doses (5-Fluorouracil 500mg/m², Doxorubicin 500 mg/m², Cyclophosphamide 500 mg/m²) and schedules (day 1 and repeated every 6-8 weeks) of chemotherapy application. In this study node positive patients were also included, in which taxanes are indicated. The german ZORO-study [2] included adequate and modern chemotherapy regimens including taxanes in 60 pts. with hormone insensitive tumors. The menstruation rate in the Goserelin and observation arm after 6 months amounted to 70.0 respectively 58.6% ($p = 0.4219$). After two years of follow up all evaluable patients of both arms reported resumed ovarian function. In the third randomized trial from Florida [3] with 49 patients and Triptorelin the menstruation resumed at 6, 12 and 18 months of chemotherapy in the respective groups (Triptorelin vs. control) as follow: 44% vs. 60%, 83% vs. 79% and 88% vs. 84%.

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GnRHa: Observation Studies (19/22)

Further information:

Four observational studies reported an ovarian protektiv effekt of GnRHa. All concluded, that GnRH-a prevent ovarian function. Chemotherapy ranged from CMF, anthracycline-based until high-dose chemotherapy regimens. Especially in patients younger than 40 years nearly 90 % of all pts reported resumption of ovarian function. In pts. older than 40 years reappearance of ovary function was reported in only 50, although the recieved an ovarian protection. It is also seen that the real number of pregnancies and moreover living births were very low [1-5] .

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Trials with Aromatase Inhibitors (20/22)

Further information:

There are differences between the trials investigating aromatase inhibitors in the adjuvant setting in terms of time of randomization and duration of therapy.

In IES, ARNO and ITA (a small trial), patients who remained disease-free after 2-3 years of tamoxifen entered the trial and were randomized to stay on tamoxifen or switch to an AI (exemestane or anastrozole). So this is a selected population that excludes patients with early recurrence = higher-risk disease, and selects patients with endocrine-responsive disease.

In ABCSG8, ATAC and BIG, patients were randomized upfront to tamoxifen for 5 years or to treatment with tamoxifen/AI (or an AI for 5 years in BIG/ATAC). In MA.17, NSABP-B33 and ABCSG 6a the duration of therapy exceeded the 5 years and was between 8 and 10 years.

There are also other differences in patient populations among these trials. It's important to bear the patient population in mind when looking at the results.

No references

Aromatase Inhibitors in Adjuvant Therapy (21/22)

No further information

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Aromatase Inhibitors in Adjuvant Therapy. Overview over Published Trials: Switching/Sequential trials (22/22)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Adjuvant Cytotoxic and Targeted Therapy

Adjuvant Cytotoxic and Targeted Therapy

- **Version 2002:**
Möbus / Nitz
- **Versionen 2003–2013:**
Harbeck / Jackisch / Janni / Loibl / von Minckwitz / Möbus / Müller / Nitz Schneeweiss / Simon / Solomeyer / Stickeler / Thomssen
- **Version 2014:**
Untch / von Minckwitz

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Subtype-specific General systemic Strategies

AGO

HR+/HER2- and “low risk”:

- Endocrine therapy without chemotherapy

++

HR+/HER2- and “high risk”

- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated in case of high tumor burden
- Followed by endocrine therapy

++

+

++

HER2+

- Trastuzumab plus
 - Sequential A/T-based regimen with concurrent T + H
 - Anthracycline-free, carboplatin-cont. regimen
 - Dose dense & escalated in case of high tumor burden

++

++

+

+

TNBC

- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated

++

+

**In case of indication for chemotherapy, consider
neoadjuvant approach**

++

Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview

Oxford / AGO
LoE / GR

➤ **Anthracyclines
(instead of CMF)**

1a A ++

➤ **Taxanes**

1a A ++

➤ **Dose-dense
(node-positive disease)**

1a A ++

➤ **CMF
(instead of no therapy)**

1a A ++

➤ **EC - T (instead of FEC – T)**

1b^a A ++

Non-Anthracycline Containing Regimens without Trastuzumab

Oxford / AGO
LoE / GR

Equivalent OS efficacy to ≥ 4 x A / EC:

- | | | | |
|-----------------|----|---|-----|
| ➤ 4-6 x Pac q3w | 1b | B | +/- |
| ➤ 6 x CMF | 1a | A | +/- |

Superior OS efficacy to 4 x AC :

- | | | | |
|----------|----|---|---|
| ➤ 4 x DC | 1b | B | + |
|----------|----|---|---|

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FORSCHEN
LEHREN
HEILEN

Taxanes

Optimal Combinations and Dosages

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in der DKG e.V.

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Regimen

Oxford / AGO
LoE / GR

- | | | | | |
|-----------------------------|--|-----------------------|----------|-----------|
| ➤ EC → P_w | E₉₀C q3w x 4 → P₈₀ qw1 x 12 | 1b^a | B | ++ |
| ➤ DAC | D₇₅A₅₀C q3w x 6 | 1b | A | ++ |
| ➤ AC → P_w | A₆₀C q3w x 4 → P₈₀ qw1 x 12 | 1b | A | ++ |
| ➤ AC → D | A₆₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b | A | ++ |
| ➤ EC → D | E₉₀C q3w x 4 → D₁₀₀ qw3 x 4 | 1b^a | B | ++ |

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Further
Information

References

Recommended Taxane-Based Regimens – Standard Dose

Oxford / AGO
LoE / GR

Combination Treatment

- DAC (BCIRG 001, instead of FAC)
- DC (US Oncol., instead of AC)
- AD (E2179, instead of AC)

| | | |
|----|---|-----|
| 1b | A | ++ |
| 1b | A | + |
| 2b | B | +/- |

Sequential Treatment (Equal Duration)

- EC→Pw (GIM, instead of FEC→Pw)
- FEC → D (PACS 01, instead of FEC)
- AC → Pw (E1199, instead of AC → P3w)
- FE₆₀C → D (TACT, instead of FE₆₀C)
- AP → CMF (TACT, instead of E → CMF)
- AP → CMF (ECTO, instead of A → CMF)

| | | |
|-----------------|---|----|
| 1b ^a | B | ++ |
| 1b | B | + |
| 1b | A | ++ |
| 2b | B | - |
| 2b | B | + |

Sequential Treatment (Unequal Duration)

- AC → P (NSABP B-28, instead of AC)
- FEC → P (GEICAM 9906, instead of FEC)
- AC → D (BCIRG 005, instead of DAC)
- EC → D (WSG/AGO, instead of FE₁₀₀C)
- EC → D (ADEBAR, instead of FE₁₂₀C)
- A → D → CMF > AD → CMF (BIG 2-98, instead of A ± C → CMF)
- E → D → CMF (TAXIT 216, instead of E → CMF)

| | | |
|-----------------|---|-----|
| 1b | A | + |
| 2b | B | + |
| 1b ^a | B | ++ |
| 1b ^a | B | ++ |
| 1b ^a | B | +/- |
| 2b | B | + |
| 2b | B | +/- |

In studies with adequately dosed anthracyclines, benefit from adding taxanes seems to be small. In the sequence AC-Taxane, there is no evidence of superiority of either taxane. Next to substance-specific side-effects, weekly administration was in general less toxic (LoE 2b^a, B). In Germany, often EC (90/600) is used instead of AC.

Adjuvant Chemotherapy (Other Drugs)

**Oxford / AGO
LoE / GR**

➤ **Capecitabine containing regimen**

1a B +/-

(in case of HER2 neg., ER/PgR neg., TPN)

➤ **E-Cis-F**

2b B +/-

➤ **Gemcitabine containing regimen**

-

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Adjuvant Chemotherapy (Dose-dense and / or Dose-escalated)

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Dose-dense regimen (N +)

- dd ACP / AC-P q2w (instead of q3w)
(CALGB 9741)
- AC / ddP q1w x 12 (instead of P q3w)
- *EC / ddP q1w x 12 (instead of P q3w)
- EC/ddP q2w (instead of q3w)
- AC/ddP q1w (instead of q2w)
- ddEC q2w/ddP q1w (instead of EC q3w)
- ddE₁₂₀C₈₃₀ q2w x 6 => P q3w x 4
- ddAC→Pq2w = 6x TAC

Oxford / AGO LoE / GR

| | | |
|-----------------|---|-----|
| 1b | A | + |
| 1b | A | ++ |
| 1b | B | ++ |
| 1b ^a | A | + |
| 1b ^a | A | ++ |
| 2b ^a | B | + |
| 1b | A | +/- |
| 1b | A | +/- |

Dose-dense and dose-escalated regimen (N ≥ 4+)

- dd E-P-C q2w (instead of EC-P q3w) (AGO)

| | | |
|----|---|----|
| 1b | A | ++ |
|----|---|----|

* Extrapolated from doxorubicin trials

Adjuvant Treatment with Trastuzumab I

Oxford / AGO
LoE / GR

- **Node-positive disease**
- **Node-negative disease**
(whenever chemotherapy is considered
as adequate)
 - **> 10 mm**
 - **> 5–10 mm**
 - **≤ 5 mm**

1a A ++

1a A ++

2b B +

2b B +/-

Adjuvant Treatment with Trastuzumab II

Oxford / AGO
LoE / GR

Start of treatment

- Simultaneously with taxanes
- Sequentially up to 3 months after chemotherapy

1a A ++

1b B +

Duration

- For 1 year
- For 2 years
- For 0.5 years

1b A ++

1b^a B -

1b^a B -

Dosage

- 2 (4*) mg/kg every week
- 6 (8*) mg/kg every 3 weeks

2b B ++

2b B ++

*Loading dose

Adjuvant Trastuzumab Cardiac Monitoring for CHF

Oxford LoE: 5

GR: D

AGO: ++

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Before start of trastuzumab

- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

} Assessment
of LVEF

During trastuzumab

Regular assessment of

- Heart rate increase > 15% above individual base level
- Body weight increase ≥ 2 kg/week

} }

3 monthly assessment of LVEF

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Further
Information

References

Adjuvant Treatment with Trastuzumab: Schedules

**Oxford / AGO
LoE / GR**

Simultaneously

- | | | | |
|---|-----------------------|----------|------------|
| ➤ With paclitaxel / docetaxel after AC / EC | 1b | A | ++ |
| ➤ With P q1w 12 x without A in pT (< 3 cm), pN0 | 2b^a | B | +/- |
| ➤ With docetaxel and carboplatin | 1b | A | + |
| ➤ With anthracyclines | 2b | B | +/- |
| ➤ With taxanes dose-dense | 2b | B | + * |

Radiotherapy concurrent with Trastuzumab **2b** **B** **+**

*** Study participation recommended**

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Adjuvant Therapy with Other Targeted Agents

Oxford / AGO
LoE / GR

➤ Lapatinib

➤ (delayed adjuvant treatment)

5 D -

1b B -

➤ Pertuzumab

5 D -

➤ Bevacizumab

1b^a B --

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Adjuvant Cytotoxic and Targeted Therapy (2/14)

Further information:

Screened data bases:

Pubmed 2003 – 2013, ASCO 2006 – 2013, SABCS 2006 – 2013, ECCO (n.d.), EBCC (n.d.). Cochrane data base (2007-2013)

Screened guidelines:

Consensus on the primary therapy of early breast cancer (St. Gallen 2007, 2009, 2011, 2013):

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Goldhirsch et al, Ann Oncol. 2009 Aug;20(8):1319-29.

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1. Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013; 24: 2206–2223.

- NCCN 2013: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Download 24. Jan 2011)

- NCI: http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page7#Section_519

- <http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/> (Download 24. Jan 2011)

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Subtype-specific General Systemic Strategies (3/14)

Further information:

In patients with HR+/HER2- and “low risk” the treatment of choice is endocrine therapy without chemotherapy

In patients with HR+/HER2- and “high risk” the recommended treatment is conventionally dosed AT-based chemotherapy or dose dense & escalated regimens in case of high tumor burden followed by endocrine therapy

In patients with HER2+ disease Trastuzumab is recommended for one year plus

- Sequential A/T-based regimen with concurrent T + H
- Or an anthracycline-free, carboplatin-containing regimen
- Or dose dense & escalated in case of high tumor burden
- In patients with TNBC the treatment contains conventionally dosed AT-based chemotherapy
- Or dose dense & escalated chemotherapy

In case of an indication for chemotherapy, the neoadjuvant approach should be considered

No references

Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview (4/14)

Further information:

CMF should be given at a dosage of C 600 mg/m² d1+8 q4w i.v., alternatively the classical oral application can be chosen with C 100 mg/m² d1-14 p.o. q4w. The three-weekly administration implies an underdosing, because a dose of CMF less than 85 % of the conventional dosage leads to a reduction of the efficacy (Bonadonna 1995). Similar conclusions can be drawn from the data of a study in the metastatic setting (Engelmann 1991) and in an older metaanalysis (Hryniuk 1986). Therefore, CMF at a dosage of 600/40/600 mg/m² q3w is regarded as not adequate.

If the indication for adjuvant chemotherapy is given after evaluation of risk, potential benefits and side effects, an anthracycline-based combination chemotherapy is regarded as minimum standard treatment. As shown in a meta-analysis, there is a reduction of the relapse rate (ratio 0.89, p=0.0001) and mortality (ratio 0.84, p<0.001) compared with adjuvant CMF-therapy after 15 years (EBCTCG, Lancet 2005).

In general, by adding a taxane in most studies disease-free survival and overall survival can further be improved. The corresponding relative reduction of risk is rather dependent from tumor biology than from nodal status and extent of disease. (Hayes, Albain). In trials adding four separate cycles of a taxane to a fixed anthracycline-based control regimen, breast cancer mortality was reduced (RR 0.86, p=0.0005; EBCTCG Lancet 2012)

The EBCTCG meta-analysis demonstrates a continuous benefit for the taxanes from year 1 to 10 in contrast to the much shorter lasting effect of the anthracyclines (EBCTCG, Lancet 2012)

In the major studies that evaluated the role of adjuvant trastuzumab in patients with HER2-overexpression, a benefit of trastuzumab was shown also with taxane containing regimens. This current evidence is discussed in the context of trastuzumab treatment (see slide 10-13).

Dose-dense (q2w) adjuvant chemotherapeutic schedules improve the relapse-free and overall survival compared to conventional adjuvant treatment options (Bonilla 2010, Moebus 2010, Citron 2003). Dose-dense and dose-intensive chemotherapeutic options improve the relapse-free and overall survival compared to conventional chemotherapy independent of the hormone receptor status if at least four lymph nodes are involved (Moebus 2010).

Anthracyclines followed by Taxane sequences have traditionally included 5 Fluorouracil in the first part of the sequence. A large randomised phase 3 study presented as an abstract at the Aa Antonio Meeting 2013 has shown that 5 FU does not have to be an integral part of the anthracycline combination (EC→T equal to FEC→ T).

Interaction between molecular breast cancer types and choice of chemotherapy.

Recent retrospective subgroup analyses of major prospective trials suggest differential efficacy of CMF, anthracycline combinations and taxanes containing regimen in triple-negative tumors, HER2-overexpressing tumors and luminal A and B tumors.

- Patients with luminal A tumors might not benefit from adjuvant chemotherapy.
- Patients with luminal B tumors should benefit from adjuvant chemotherapy, it is unclear whether addition of anthracyclines is necessary.
- Patients with HER2-type tumors will benefit from therapies that contain both, anthracyclines and taxanes.
- Patients with triple-negative tumors also seem to benefit from both, anthracyclines and taxanes. However, also CMF and platinum-containing regimen may be effective.

Caveats:

Molecular typing is based on molecular genetic testing. Immunohistochemical results correlate in only 70% of the tumors. There is no clear data, how luminal A and B can be distinguished by immunohistochemistry. Probably the most practical approach is the measurement of Ki-67 with a sensitivity and specificity of Ki-67 of about 80%

Other markers e.g. uPA/PAI-1 or RANKL are also discussed as suitable discriminators of luminal A and B type cancers. In addition, prospective validation of the interaction between choice of chemotherapy and molecular typing is lacking.

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Statement 5 FU

Epirubicin and cyclophosphamide (EC) followed by paclitaxel (T) versus fluorouracil, epirubicin and cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the Gruppo Italiano Mammella (GIM)-2 randomized phase III study Cognetti F, Bruzzi P, De Placido S, De Laurentiis M, Boni C, Aitini E, Durando A, Turetti A, Valle E, Garrone O, Puglisi F, Montemurro F, Barni S, Di Blasio B, Gamucci T, Colantuoni G, Olmeo N, Tondini C, Parisi AM, Bighin C, Pastorino S, Lambertini M, Del Mastro L. I.F.O. Istituto Regina Elena e Istituto San Gallicano - Mostacciano, Roma, Italy; IRCCS AOU San Martino-IST, Genova, Italy; Università degli Studi di Napoli Federico II, Napoli, Italy; Istituto Nazionale Tumori - IRCCS Fondazione Pascale, Napoli, Italy; Arcispedale S. Maria Nuova-IRCCS, Reggio Emilia, Italy; Ospedale di Mantova, Mantova, Italy; Città della Salute e della Scienza - ASO OIRM S Anna, Torino, Italy; Ospedale Evangelico Valdese - ASLTO1, Torino, Italy; Ospedale Businco, Cagliari, Italy; Oncologia ASO S. Croce e Carle, Cuneo, Italy; Azienda Ospedaliero Universitaria - Santa Maria della Misericordia, Udine, Italy; IRCCS Candiolo, Candiolo (Torino), Italy; Azienda Ospedaliera Treviglio, Treviglio (Bergamo), Italy; Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; Unità Operativa Complessa di Oncologia della ASL di Frosinone, Frosinone, Italy; A.O.R.N. "S.G. Moscati", Avellino, Italy; UOC Oncologia Medica Ospedale Civile, Sassari, Italy; Ospedale Papa Giovanni XXIII, Bergamo, Italy; Ospedale S. Camillo-Forlanini, Roma, Italy. San Antonio Breast Cancer Symposium 2013. S5-06.

Statement KI 67

Prognostic Value of a Combined Estrogen Receptor, Progesterone Receptor, Ki-67, and Human Epidermal Growth Factor Receptor 2 Immunohistochemical Score and Comparison With the Genomic Health Recurrence Score in Early Breast Cancer

Jack Cuzick, Mitch Dowsett, Silvia Pineda, Christopher Wale, Janine Salter, Emma Quinn, Lila Zabaglo, Elizabeth Mallon, Andrew R. Green, Ian O. Ellis, Anthony Howell, Aman U. Buzdar, and John F. Forbes. Published Ahead of Print on October 11, 2011 as 10.1200/JCO.2010.31.2835

Non-Anthracycline Containing Regimens without Trastuzumab (5/14)

Further information:

The efficacy of CMF has been shown in numerous single studies with a long term follow up of meanwhile up to 20 years and has been proven in metaanalysis (Bonadonna 1995, EBCTCG 2005). Therefore, six cycles of CMF can be given in patients with contraindications for anthracycline-containing regimens. If considering all risks (cardiac toxicity, secondary leucemia), an anthracycline-containing regimen seems to be contraindicated, an anthracycline-free combination can be chosen (Jones 2006, Jones 2009). However, the comparator arm in the US Oncology trial was merely 4xAC. Ongoing clinical trials are currently evaluating the role non-anthracycline regimens in comparison to triplet combinations or anthracycline-taxane sequences. The CALGB B 40101 phase III study showed in a 2x2 factorial design for patients with 0 to 3 positive lymph nodes no benefit for extended treatment with 6 x AC or T over 4 x AC or T, respectively (Shulman et al, 2012).

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Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2005 May 14-20;365(9472):1687-717

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Six cycles of doxorubicin and cyclophosphamide or paclitaxel are not superior to four cycles as adjuvant chemotherapy for breast cancer in women with zero to three positive axillary nodes: Cancer and Leukemia Group B 40101. Shulman LN, Cirincione CT, Berry DA, Heather PB, Perez EA, O'Regan R, Martino SM, Atkins JN, Mayer EM, Schneider CE, Kimmick G, Norton L, Muss H, Winer EP, Hudis C. J Clin Oncol. 2012 Nov 20;30(33):4071-6. Doi:10.1200/JCO406405. http://www.ncbi.nlm.nih.gov/pubmed/22826271?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Further information

Four cycles of anthracycline with cyclophosphamide at threeweekly intervals (4 x AC or EC) followed by 12 cycles of weekly Paclitaxel is superior to threeweekly Paclitaxel in node negative and node positive patients.

Six cycles of Docetaxel Anthracycline and Cyclophosphamide (TAC) at threeweekly intervals is superior to six cycles of FAC at threeweekly intervals. TAC has to be given with bone marrow stimulating growth factors and prophylactic antineoplastic drugs to avoid febrile neutropenia

Four cycles of anthracycline cyclophosphamide (AC or EC) at threeweekly intervals, followed by four cycles of Docetaxel 100, given at threeweekly intervals without growth factor support is equally effective to six cycles of TAC.

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Weekly paclitaxel in the adjuvant treatment of breast cancer.

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Phase III Study of Doxorubicin/Cyclophosphamide With Concomitant Versus Sequential Docetaxel As Adjuvant Treatment in Patients With Human Epidermal Growth Factor Receptor 2–Normal, Node-Positive Breast Cancer: BCIRG-005 Trial. Wolfgang Eiermann, Tadeusz Pienkowski, John Crown, Saeed Sadeghi, Miguel Martin, Arlene Chan, Mansoor Saleh, Sandeep Sehdev, Louise Provencher, Vladimir Semiglazov, Michael Press, Guido Sauter, Mary-Ann Lindsay, Alessandro Riva, Marc Buyse, Philippe Drevot, Henry Taupin, and John R. Mackey. J Clin Oncol 29:3877-3884.

Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. Henderson IC, Berry DA, Demetri GD, Cirincione CT, Goldstein LJ, Martino S, Ingle JN, Cooper MR, Hayes DF, Tkaczuk KH, Fleming G, Holland JF, Duggan DB, Carpenter JT, Frei E 3rd, Schilsky RL, Wood WC, Muss HB, Norton L. J Clin Oncol. 2003 Mar 15;21(6):976-83.

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Taxanes: Optimal Combination and Dosage (6/14)

Further information:

In patients with node-positive disease, taxane-containing regimens improve the relapse-free survival (Mamounas 2005, Martin 2005, Bianco 2006) and overall survival (Henderson 2003, Martin 2005, Roche 2006, Bria 2006, Ferguson 2007, De Laurentiis 2008) compared to taxane-free protocols. Docetaxel in a sequential schedule at standard dose seems to reveal superior benefit compared to docetaxel in combination with the anthracycline in reduced dosage (Crown 2006). No consistent superiority was demonstrated in most prospective studies with taxane-containing schedules versus taxane-free regimen in node-negative patients (Gianni 2005, Goldstein 2005, Jones 2006) except for one trial.

In the sequence AC followed by a taxane, both taxanes are equally effective; however, the weekly administration of paclitaxel offers a better DFS and OS compared to the three-weekly regimen with acceptable toxicity (Sparano 2008). Some of the large prospective trials like the Sparano trial and others have included about 30 % patients with high risk, node negative disease.

References:

See references to 5/14

Recommended Taxane-Based Regimens – Standard Dose (7/14)

Further information:

In patients with node-positive disease, taxane-containing schedules improve the relapse-free survival (Mamounas 2005, Martin 2005, Bianco 2006) and overall survival (Henderson 2003, Martin 2005, Roche 2006, Bria 2006, Ferguson 2007, De Laurentiis 2008) compared to taxane-free protocols. Docetaxel in a sequential schedule at standard dose seems to reveal superior benefit compared to docetaxel in combination with the anthracycline in reduced dosage (Crown 2006). No superiority was demonstrated in most prospective studies with taxane-containing schedules versus taxane-free regimen in nodal-negative patients (Gianni 2005, Goldstein 2005, Jones 2006) except for one trial not published as full paper (Martin 2008), see also comment in slide 3. The EBCTCG Meta-analysis based on 100.000 women in 123 randomised trials confirmed the superiority for the addition of taxanes to a fixed anthracycline-based regimen (RR 0.86, $p=0.0005$). The proportional risk reductions were minimally affected by age, nodal status, tumor size or differentiation, (Lancet 2012). Taxanes can be used as combinations

TAC instead of FAC (BCIRG 001 study)

DC instead of AC (US Oncology study)

or AD instead of AC (E 2179 study)

Or as sequential treatment of equal duration like

EC→P weekly instead of FEC→P weekly (GIM trial, Cignetti 2013)

FEC→Docetaxel instead of 6 X FEC (PACS 01 study)

AC→P weekly instead of P threeweekly (E 1199 study, Sparano)

FEC→Docetaxel instead of FEC (TACT study)

FEC→Docetaxel instead of E→CMF (TACT study)

AP→CMF instead of A→CMF (ECTO study)

Phase III Trial Evaluating the Addition of Paclitaxel to Doxorubicin Followed by Cyclophosphamide, Methotrexate, and Fluorouracil, As Adjuvant or Primary Systemic Therapy: European Cooperative Trial in Operable Breast Cancer. Luca Gianni, Jose' Baselga, Wolfgang Eiermann, Vincente Guillem Porta, Vladimir Semiglazov, Ana Lluh, Milvia Zambetti,

Dolores Sabadell, Gu'nther Raab, Antonio Llombart Cussac, Alla Bozhok, Angel Martinez-Agullo', Marco Greco, Mikhail Byakhov, Juan Jose` Lopez Lopez, Mauro Mansutti, Pinuccia Valagussa, and Gianni Bonadonna. J Clin Oncol 2009. 27:2474-2481.

Or sequential treatment of unequal duration

AC→P instead of AC (NSABP B 28)

Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28. Eleftherios P. Mamounas, John Bryant, Barry Lembersky, Louis Fehrenbacher, Scot M. Sedlacek, Bernard Fisher, D. Lawrence Wickerham, Greg Yothers, Atilla Soran, and Norman Wolmark. Clin Oncol 2005. 23:3686-3696.

FEC → P instead of FEC (GEICAM 9906 study) Martin et al., J Natl Cancer Inst. 2008; 100(11):805-814)

AC→ D instead of TAC (BCIRG 005 study) see above: Eiermann et al

EC→D instead of FEC (WSG/ AGO study)

EC→D instead of FEC (ADEBAR study),

A(D) →D→CMF instead of A(C) →CMF (BIG 2-98 study)

E→D→CMF instead of E→CMF (TAXIT study)

In the sequence AC followed by a taxane, both taxanes are equally effective; however, the weekly administration of paclitaxel offers a better DFS and OS with acceptable toxicities compared to the three-weekly regimen in patients with node positive and high risk node negative disease (Sparano 2008).

A current meta-analysis of phase III trials for 8728 patients receiving sequential or concurrent anthracyclines and taxanes revealed significant differences in favor of the sequential regimens in regards to DFS (RR: 0.90, p=0.01) as well as OS (RR: 0.88; p = 0.02), respectively (Shao et al. 2012).

References (see also references to 5/14 and 6/ 14):

Sequential versus concurrent anthracyclines and taxanes as adjuvant chemotherapy of early breast cancer: a meta-analysis of phase III randomized control trials.

Shao N, Wang S, Yao C, Xu X, Thang Y, Zhang Y, Lin Y,
Breast 2012 Jun;21(3):389-93. Doi 10.1016/j.breast.2012.03.011.
[http://www.ncbi.nlm.nih.gov/pubmed/22542064?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPa
nel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/22542064?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

Adjuvant Chemotherapy (Other Drugs) (8/14)

Further information:

Capecitabine, gemcitabine and platin have been investigated in adjuvant trials. So far none of these drugs can be recommended to be included into anthracycline/taxane based regimen. One phase III trial investigated capecitabine and docetaxel followed by FEC versus weekly paclitaxel followed by FEC. After 50 months of follow-up no differences in regards to relapse free survival were seen (Kelly et al. 2012). Besides these first findings, numerous trials are still ongoing and the final results need to be awaited for the coming years. High risk populations or TNBC might benefit from the addition of Capecitabine. However, those data are not sound enough to base recommendations on it. However, a first meta-analysis of 4107 patients in two trials (USO and FinXX) reported a significant improvement by the addition of capecitabine to anthracycline and taxan based adjuvant therapy in regards to DFS (HR = 0.83, p = 0.027), OS (HR = 0.71, p = 0.008) and distant recurrence (HR = 0.79, p = 0.008) respectively. The subgroup analyses revealed a special benefit for triple negative, hormone receptor negative and Her2/neu negative patients (Jiang et al. 2012).

References:

Gemcitabine in adjuvant trials

Wardley AM, Hiller L, Howard HC, Dunn JA, Bowman A, Coleman RE, Fernando IN, Ritchie DM, Earl HM, Poole CJ; tAnGo Trial Collaborators.

tAnGo: a randomised phase III trial of gemcitabine in paclitaxel-containing, epirubicin/cyclophosphamide-based, adjuvant chemotherapy for early breast cancer: a prospective pulmonary, cardiac and hepatic function evaluation.

Br J Cancer. 2008 Aug 19;99(4):597-603. Epub 2008 Jul 29

C. J. Poole, L. Hiller, H. C. Howard, J. A. Dunn, P. Canney, A. M. Wardley, M. J. Kennedy, R. E. Coleman, R. C. Leonard, H. M. Earl, tAnGo trial collaborators. tAnGo: A randomized phase III trial of gemcitabine (gem) in paclitaxel containing, epirubicin/cyclophosphamide-based, adjuvant chemotherapy (CT) for women with early-stage breast cancer

(EBC). - ASCO 2008; J Clin Oncol 26: 2008 (May 20 suppl; abstr 506).

http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34423

Capecitabine in Adjuvant Trials

| Adj trials | Pts, n | Test arm | Control | Primary endpoint | Results |
|-------------|--------|---------------------|---------------------------|------------------|--------------------------|
| FinXX | 1,500 | CDX3→CycECX3 | DX3→CycEFX3 | 5-year RFS | 86.6 vs 84.1; p=0.09 |
| | | | | 5-year OS | 92.6 vs. 89.7; p=0.08 |
| US Oncology | 2,611 | ACycX4→CDX4 | ACycX4→DX4 | 5-year DFS | 89% vs 87%: p=0.125 |
| | | | | 5-year OS | 94% vs 92%; p=0.011 |
| TACT2 | 4,400 | EX4→CX4 | EX4→CMFX4 | 5-year DFS | Follow-up |
| GEICAM | 1,382 | EDX4→CX4 | ECycX4→DX4 | 5-year DFS | Follow-up |
| GAIN | 3,028 | ECycX4→CPX4 | EX3→PX3→CycX3 | EFS | Follow-up |
| MINDACT | 6,600 | ACX6 | AnthracyclineX6 | 5-year DFS | recruiting |
| CIBOMA | 876 | ACyc/FECyc/AD→CX8 | ACyc/FECyc/AD | 5-year DFS | Follow-up |
| JBCRG04 | 900 | CX8 ± endoc.therapy | Observation ± endocr. th. | DFS | Follow-up |
| ICE | 1,500 | Ibandronate +CX6 | Ibandronate | EFS | Follow-up |
| CALGB-49907 | 633 | CX6 | ACycX4/CycMFX6 | RFS | follow-up |
| Shao et al. | 455 | CycECX6 | CycEFX6 | Safety | |

| | | | | | |
|--------------|-----|--------------|--------------|------------------|--|
| Kelly et al. | 601 | 4x XD→6x FEC | 12x P→6x FEC | 5year RFS PCR | 87.5 vs. 90.7 p= 0.51 19.8 vs. 16.4 p= 0.45 |
|--------------|-----|--------------|--------------|------------------|--|

So far, none of the trials could demonstrate an additional benefit of adding capecitabine to an anthracycline/taxane based therapy. However, most of the trials used lower doses of either the taxane or capecitabine in order to cope with the toxicity. In the neoadjuvant setting the addition of capecitabine did not improve the pCR rate in the Geparquattro trial but in the ABCSG 24 trial and the metanalysis of several German neoadjuvant trials. The reason for the positive results of the latter one is the correction for the necessary dose reduction of docetaxel.

D=docetaxel; Cyc=cyclophosphamide; E=epirubicin; F=5-FU; A=doxorubicin; P=paclitaxel; bev=bevacizumab; G=gemcitabine; M=methotrexate; DFS=disease-free survival; EFS=event-free survival

References Reviews and Metaanalyses:

Review of Capecitabine for the Treatment of Triple-Negative Early Breast Cancer.
Steger GG, Barrios C, O'Shaughnessy J, Martin M, Gnant M. SABCS PD01-3
www.abstracts2view.com/sabcs10/view

First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis.

Jiang Y, Yin W, Zhou L, Yan L, Zhou Q, Du Y, Shen Z, Shao Z, Lu J.

PLoS ONE 2012 7(3): e32474. Doi:10.1371/journal.pone0032474

http://www.ncbi.nlm.nih.gov/pubmed/23301067?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Adjuvant Chemotherapy (Dose-dense and/or Dose-escalated) (9/14)

Further information:

Dose-dense regimens are defined as chemotherapy schedules in which the intervals between the cycles can be shortened to a minimum (in general from three weeks to two weeks) due to the administration of granulocyte-colony stimulating substances. The principle of dose-dense schedules has been discussed for a long time (especially Skipper 1964, Goldie 1979, Frei 1980, Bonadonna 1981, Hryniuk 1986, Norton 1988). The CALGB 9741 study demonstrated for the first time in a clinical setting that administration of a dose-dense regime can achieve a relevant benefit in patients with node-positive breast cancer. Because of the short follow up period, these data cannot be considered as a basis for general recommendations (Citron 2003). As compared with standard therapy, weekly paclitaxel after standard AC chemotherapy is also associated with improved survival (Sparano 2008). Dose-dense and intensive chemotherapy schedules improve the relapse-free and overall survival compared to conventional adjuvant chemotherapy treatment plans independent of the hormone receptor status in patients with ≥ 4 lymph nodes (Moebus 2006).

In a large three arm randomised 3 trial, dose dense AC followed by Paclitaxel at twoweekly intervals was equivalent to standard threeweekly TAC (NSABP B 38 study).

Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial. Sandra M. Swain, Gong Tang, Charles E. Geyer Jr, Priya Rastogi, James N. Atkins, Paul P. Donnellan, Louis Fehrenbacher, Catherine A. Azar, Andre´ Robidoux, Jonathan A. Polikoff, Adam M. Brufsky, David D. Biggs, Edward A. Levine, John L. Zapas, Louise Provencher, Donald W. Northfelt, Soonmyung Paik, Joseph P. Costantino, Eleftherios P. Mamounas, and Norman Wolmark. J Clin Oncol 31:3197-3204

The question of efficacy and side effects of weekly Paclitaxel (Sparano like) versus twoweekly Paclitaxel (dose dense like) has been answered by a large multicentre two by two factorial trial, S 0221, with more then 1.600 patients per arm, showing no difference in DFS and OS between 12 weekly Paclitaxel 80 cycles (without growth factor support) and six twoweekly (dose dense) Paclitaxel 175 cycles with growth factor support (Comparison of two schedules of Paclitaxel for adjuvant therapy of breast cancer. G. T. Budd, W. E. Barlow, H. C. F. Moore, T. J. Hobday, J. A. Stewart, C. Isaacs, M.

Salim, J. K. Cho, K. Rinn, K. S. Albain, H. K. Chew, G. V. Burton, T. D. Moore, G. Srkalovic, B. A. McGregor, L. E. Flaherty, R. B. Livingston, D. Lew, J. Gralow, G. N. Hortobagyi). ASCO 2013

The comparison of dose dense anthracycline (4x EC) followed by Paclitaxel (4x) both q2w and standard EC followed by Paclitaxel was one important gap to be closed in the scientific debate between dose dense, dose intensified twoweekly application and standard application.

The GIM study randomised more than 2.000 node positive patients (60 % 1-3 nodes, 40 % more then 4 nodes). Dose dense EC at twoweekly intervals followed by weekly Paclitaxel was superior to threeweekly EC followed by threeweekly Paclitaxel . Most interesting, the Forrest plot showed all subgroups having a significant benefit, including those with more than 4 and more than 10 nodes (Cognetti, GIM 2 study, SABCS 2013)

High-dose chemotherapy regimens followed by autologous stem cell transplantation should only be used in the context of well-designed clinical trials (Berry 2007).

For details and references of studies see also following slide and references.

References:

Experimental evaluation of potential anticancer agents: XIII. On the criteria and kinetics associated with „curability“ of experimental leukemia. Skipper HE, Schabel FM Jr, Wilcox WS. Cancer Chemother Rep. 1964 Feb;35:1-111.
http://www.ncbi.nlm.nih.gov/pubmed/14117037?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Goldie JH, Coldman AJ. Cancer Treat Rep. 1979 Nov-Dec;63(11-12):1727-33
http://www.ncbi.nlm.nih.gov/pubmed/526911?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Dose: a critical factor in cancer chemotherapy. Frei E 3rd, Canellos GP. Am J Med. 1980 Oct;69(4):585-94.
http://www.ncbi.nlm.nih.gov/pubmed/6999898?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Dose-response effect of adjuvant chemotherapy in breast cancer. Bonadonna G, Valagussa P. N Engl J Med. 1981 Jan 1;304(1):10-5.
http://www.ncbi.nlm.nih.gov/pubmed/7432433?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. Hryniuk W, Levine MN. J Clin Oncol. 1986 Aug;4(8):1162-70.
http://www.ncbi.nlm.nih.gov/pubmed/3525765?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

A Gompertzian model of human breast cancer growth. Norton L. Cancer Res. 1988 Dec 15;48(24 Pt 1):7067-71.
http://www.ncbi.nlm.nih.gov/pubmed/3191483?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Statement: dd ACP / AC-P q2w (instead of q3w)

Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. Citron ML, Berry DA, Cirincione C, Hudis C, Winer EP, Gradishar WJ, Davidson NE, Martino S, Livingston R, Ingle JN, Perez EA, Carpenter J, Hurd D, Holland JF, Smith BL, Sartor CI, Leung EH, Abrams J, Schilsky RL, Muss HB, Norton L. J Clin Oncol. 2003 Apr 15;21(8):1431-9. Epub 2003 Feb 13. Erratum in: J Clin Oncol. 2003 Jun 1;21(11):2226.
[http://www.ncbi.nlm.nih.gov/portal/utils/pagereolver.fcgi?log\\$=activity&recordid=1229960991941230](http://www.ncbi.nlm.nih.gov/portal/utils/pagereolver.fcgi?log$=activity&recordid=1229960991941230)

Five year follow-up of INT C9741: dose-dense (DD) chemotherapy (CRx) is safe and effective. Hudis C, Citron M, Berry D, Cirincione C, Gradishar W, Davidson N, Martino S, Livingston R, Ingle J, Perez E, Abrams J, Schilsky R, Ellis M, Muss H, Norton L, Winer E. San Antonio Breast Cancer Symposium 2005, Abstract 41

http://www.abstracts2view.com/sabcs05/view.php?nu=SABCS05L_372&terms=

Statement: AC / ddP q1w x 12 (instead of p q3w)

http://www.ncbi.nlm.nih.gov/pubmed/6999898?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Weekly paclitaxel in the adjuvant treatment of breast cancer.

Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr, Wood WC, Davidson NE. N Engl J Med. 2008 Apr 17;358(16):1663-71. Erratum in: N Engl J Med. 2008 Jul 3;359(1):106.

http://www.ncbi.nlm.nih.gov/pubmed/18420499?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Statement: dd E-P-C q2w (instead of EC-P q3w)

Ten year follow-up analysis of intense dose-dense adjuvant epirubicin (E), paclitaxel (T) and cyclophosphamide (C) (iddETC) confirms superior DFS and OS benefit in comparison to conventional dosed chemotherapy in high-risk breast cancer patients with ≥ 4 positive lymph nodes. Volker J Moebus, A Schneeweiss, A du Bois, H.-J. Lueck, H Eustermann, W Kuhn, C Kurbacher, U Nitz, R Kreienberg, C Jackisch, J Huober, C Thomssen and M Untch. San Antonio Breast Cancer Symposium 2012, Abstract S3-4

Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk breast cancer patients ($\geq 4+$ LN): Mature results of an AGO-phase-III study. Moebus VJ, Jackisch C, Lueck HJ, du Bois A, Thomssen C, Kurbacher C, Kuhn W, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Kreienberg R, Konecny GE, Untch M.). J Clin Oncol 10;28(17):2874-80. Epub 2010 May 10 <http://jco.ascopubs.org/content/28/17/2874.long>

Statement: ddE120C830 q2w x 6 => P q3w x 4E

TACT2

The UK TACT2 Trial: Comparison of Standard vs Accelerated Epirubicin in Patients Requiring Chemotherapy for Early Breast Cancer (EBC) (CRUK/05/019).

Cameron D, Barrett-Lee P, Canney P, Banerji J, Bartlett J, Bloomfield D, Bowden S, Brunt M, Earl H, Ellis P, Fletcher M, Morden JP, Robinson A, Sergenson N, Stein R, Velikova G, Verrill M, Wardley A, Coleman R, Bliss JM. SABCS 2012(abs S3-3).

Statement: High-dose regimen (N ≥ 10+)

No further information

References Dose Density: Overview over Published Phase III Trials with N > 1000

| Trial | Source | Ind | Treatment | N | F/U mo | DFS/EFS | OS | Remarks |
|------------|----------------|-------|---|------|-----------|---|--|-----------------------------|
| CALGB 9741 | Citron 2003 | N+ | 4xA ₆₀ → 4xP ₁₇₅ → 4xC vs 4xA ₆₀ C → 4xP ₁₇₅ q2w vs q3w | 2005 | 36 | q2 vs q3w HR 0.74, p=0.010 seq vs con HR 0.93, p=0.58 | q2 vs q2w HR 0.69, p=0.013 seq vs con HR 0.89, p=0.48 | ER+ vs ER- HR 0.18, p<0.01; |
| CALGB 9741 | Hudis 2005 | N+ | 4xA ₆₀ → 4xP ₁₇₅ → 4xC vs 4xA ₆₀ C → 4xP ₁₇₅ q2w vs q3w | 1938 | 36 | q2 vs q2w ER+ ns ER- p=0.014 | q2 vs q2w ER+ ns ER- p=0.039 | restrospective analysis |
| AGO | Moebus 2006 | N≥4+ | 3xE ₁₅₀ → 3xP ₂₂₅ → 3xC ₂₅₀₀ q2w vs 4xE ₉₀ C ₆₀₀ → 4xP ₁₇₅ q3w | 1284 | 62 | HR 0.72, p<0.01 | HR 0.76, p=0.029 | |
| GONO-MIG | Venturini 2005 | N+/N- | 6xFE ₆₀ C q3w vs 6 xFE ₆₀ C q2w | 1214 | 125 | EFS HR 0.88, p=0.31 | HR 0.87, p=0.35 | |
| E1199 | Sparano 2007 | N+/N- | 4xA ₆₀ C → 4xP ₁₇₅ q3w vs 4xA ₆₀ C → 12xP ₈₀ qw vs 4xA ₆₀ C → 4xD ₁₀₀ q3w | 4950 | 64 | P3 vs P1 HR 1.27, p=0.006 P3 vs D3 HR 1.23, p=0.02 P3 vs D1 HR 1.09, ns | P3 vs P1 HR 1.32, p=0.01 P3 vs D3 HR 1.13, p=ns P3 vs D1 HR 1.02, ns | |

| | | | | | | | | |
|---------------------|-----------------|-------|--|------|----|---|----|-----------------------------|
| | | | vs 4xA ₆₀ C → 12xD ₃₅ qw | | | | | |
| NCIC CTG MA21 | Burnell 2006 | N+/N- | 6xCE ₁₂₀ F vs 6xE ₁₂₀ C q2w → 4xP q3w vs 4xA ₆₀ C q3w → 4xP q3w | 2104 | 30 | AC-P vs CEF HR 1.49, p=0.005 AC-P vs ddEC-P HR 1.68, p=0.006 ddEC-P vs CEF HR 0.89, ns | ND | no difference in ER+ pts |

A, doxorubicin; C, cyclophosphamide; con, concurrent; D, Docetaxel; DFS, disease-free survival; E, epirubicin; EFS, event-free survival; ER, estrogen receptor; F/U, follow-up; HR, hazard ratio; ns, not significant; OS, overall survival; P, paclitaxel; q2w, two weekly; q3w, three weekly; seq, sequential; vs, versus.

Metaanalysis:

Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. J Natl Cancer Inst. 2010 Dec 15;102(24)

Adjuvant Treatment with Trastuzumab I (10/14)

Further information:

All studies demonstrating a benefit for adjuvant trastuzumab therapy included node-negative and node-positive patients and subgroup analysis showed a benefit for both groups of patients. Therefore, trastuzumab-containing regimens should be also used in node-negative patients with risk factors.

References for use of trastuzumab and further information see also slide “Adjuvant Treatment with Trastuzumab (2)”.

Limited data suggests that also patients with HER2-positive tumors smaller than 1cm have a substantially increased risk of recurrence compared to patients with non-amplified tumors. Since benefit from trastuzumab in the adjuvant studies was also observed independent of tumor size, the use of trastuzumab also needs to be considered in small tumors. Therefore, in patients with tumors > 5 mm and risk factors in addition to HER2 overexpression/gene amplification who are also candidates for adjuvant chemotherapy, the use of Trastuzumab can be considered.

References:

Statements: “node-positive” and “node-negative”

See following slides

Reference for “Disease with additional risk factors and tumors <1 cm“

High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakhit R, Cardoso F, Peintinger F, Hanrahan EO, Sahin A, Guray M, Larsimont D, Feoli F, Stranzl H, Buchholz TA, Valero V, Theriault R, Piccart-Gebhart M, Ravdin PM, Berry DA, Hortobagyi GN. J Clin Oncol. 2009 Dec 1;27(34):5700-6. Epub 2009 Nov 2.

Adjuvant Treatment with Trastuzumab II (11/14)

Further information

In three trials (Romond 2005, Piccart-Gebhart 2005, Smith 2007, Slamon 2006) trastuzumab has been administered for one year. 2-year treatment was not superior to one year in the HERA-trial despite a transient advantage in DFS for the 2-year arm in the hormone receptor negative cohort (Goldhirsch 2012). The PHARE-trial failed to show that 6 months of trastuzumab is non inferior to 12 months. Subgroup analysis suggested that sequential modality for ER negative tumors impacted the overall results while results in other groups seemed compatible with non-inferiority hypothesis (Pivot 2012). In a much smaller randomized study (FinHer; 232 patients) trastuzumab given simultaneously to chemotherapy for only nine weeks reduced hazard ratios for relapse (0.46, $p=0.0078$) and distant metastases (0.43, $p=0.0078$), respectively (Joensuu 2006).

As a sequential therapy in the HERA trial (Piccart-Gebhart 2005, Smith 2007), patients received different regimens containing anthracyclines with or without taxanes and trastuzumab after completion of chemotherapy.

All other studies applied taxanes simultaneously with trastuzumab. The fully published study (Romond 2005) combined analysis of the two US trials and used paclitaxel either weekly or three-weekly in combination with trastuzumab after four cycles of AC.

Based on the published registration trials, both options (sequential and concurrent use of trastuzumab) are possible. Yet, recent evidence (Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. Edith A. Perez, Vera J. Suman, Nancy E. Davidson, Julie R. Gralow, Peter A. Kaufman, Daniel W. Visscher, Beiyun Chen, James N. Ingle, Shaker R. Dakhil, JoAnne Zujewski, Alvaro Moreno-Aspitia, Thomas M. Pisansky, and Robert B. Jenkins. J Clin Oncol 29:4491-4497. 2011) suggests a substantial numerical advantage of concurrent use of trastuzumab with a taxane vs. sequential administration even though the p-value is not significant after correction for multiple testing as stated in the study protocol. Thus, concurrent use is preferable.

An additional study used an anthracycline-free regimen of docetaxel and carboplatin with similar efficacy as AC followed by docetaxel and trastuzumab (Slamon 2011).

All studies included node-negative patients and subgroup analysis showed also a benefit for these patients. Therefore, taxane-based regimens can be considered also in node-negative patients.

References:

Reference for statement “Start of treatment up to 3 months after chemotherapy“

Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Gøtzes V, Ward C, Strähle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. N Engl J Med. 2005 Oct 20;353(16):1659-72.

2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sánchez Rovira P, Piccart-Gebhart MJ; HERA study team.

Lancet. 2007 Jan 6;369(9555):29-36.

HERA TRIAL:

2 years versus 1 year of adjuvant trastuzumab for

HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Aron Goldhirsch, Richard D Gelber, Martine J Piccart-Gebhart, Evandro de Azambuja, Marion Procter, Thomas M Suter, Christian Jackisch, David Cameron, Harald A Weber, Dominik Heinzmann, Lissandra Dal Lago, Eleanor McFadden, Mitch Dowsett, Michael Untch, Luca Gianni, Richard Bell, Claus-Henning Köhne, Anita Vindevoghel, Michael Andersson, A Murray Brunt, Douglas Otero-Reyes, Santai Song, Ian Smith, Brian Leyland-Jones*, Jose Baselga*, for the Herceptin Adjuvant (HERA) Trial Study Team. www.thelancet.com Published online July 18, 2013 [http://dx.doi.org/10.1016/S0140-6736\(13\)61094-6](http://dx.doi.org/10.1016/S0140-6736(13)61094-6)

PHARE Trial Results of Subset Analysis Comparing 6 to 12 Months of Trastuzumab in Adjuvant Early Breast Cancer Pivot X, Romieu G, Bonnefoi H, Pierga J-Y, Kerbrat P, Guastalla J-P, Lortholary A, Espié M, Fumoleau P, Khayat D, Pauporte I, Kramar A. SABCS 2012 (abs S5-3).

6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, Lortholary A, Espié M, Fumoleau P, Serin D, Jacquin JP, Jouannaud C, Rios M, Abadie-Lacourtoisie S, Tubiana-Mathieu N, Cany L, Catala

S, Khayat D, Pauporté I, Kramar A; PHARE trial investigators. *Lancet Oncol.* 2013 Jul; 14(8):741-8. doi: 10.1016/S1470-2045(13)70225-0. Epub 2013 Jun 11.

References for statement “Start of treatment simultaneously with taxanes or platin/docetaxel “

Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials.

Yin W, Jiang Y, Shen Z, Shao Z, Lu J. *PLoS One.* 2011;6(6):e21030. Epub 2011 Jun 9.
<http://www.ncbi.nlm.nih.gov/pubmed/?term=Yin%20W%2C%20trastuzumab>

Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. *N Engl J Med.* 2005 Oct 20;353(16):1673-84.
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Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. Edith A. Perez, Vera J. Suman, Nancy E. Davidson, Julie R. Gralow, Peter A. Kaufman, Daniel W. Visscher, Beiyun Chen, James N. Ingle, Shaker R. Dakhil, JoAnne Zujewski, Alvaro Moreno-Aspitia, Thomas M. Pisansky, and Robert B. Jenkins. *J Clin Oncol* 29:4491-4497. 2011

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The question of anthracycline free chemotherapy with trastuzumab is still under debate

Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? Harold J. Burstein, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA Martine J. Piccart-Gebhart, Institut Jules Bordet, Brussels, Belgium. Edith A. Perez, Mayo Clinic, Jacksonville, FL. Gabriel N. Hortobagyi, MD Anderson Cancer Center, Houston, TX. Norman Wolmark, Allegheny General Hospital, National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA. Kathy S. Albain, Loyola University Chicago Stritch School of Medicine, Maywood, IL. Larry Norton, Memorial Sloan-Kettering Cancer Center, New York, NY. Eric P. Winer, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. Clifford A. Hudis, Memorial Sloan-Kettering Cancer Center, New York, NY Journal of Clinical Oncology, Vol 30, No 18 (June 20), 2012: pp 2179-2182

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A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). Tolane SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP. Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute, Nashville, TN; Massachusetts General Hospital, Boston, MA; Duke University, Durham, NC; Loyola University, Maywood, IL; University of California, San Francisco, CA; Washington University, St. Louis, MO; Long Island Jewish Medical Center, New Hyde Park, NY; Johns Hopkins University, Baltimore, MD; University of North Carolina, Chapel Hill, NC. SABCS 2013. S1-04

References for statements for “duration” and “dosage” see above

Adjuvant Trastuzumab Cardiac Monitoring for CHF (12/14)

Further information:

All clinical trials examining the adjuvant use of trastuzumab included monitoring of cardiac function by either echocardiography or MUGA scans.

An increase in cardiotoxicity in patients receiving trastuzumab in addition to chemotherapy was reported.

The NSABP B-31 5-year update identified four risk factors for heart failure in trastuzumab-treated patients:

- Age (50–59 years, 5.1%; ≥60 years, 5.4%)
- Use of hypertensive medications (6.8%)
- Baseline LVEF values of 50%–54% (12.9%)
- Post-anthracycline chemotherapy LVEF values of 50%–54% (12.6%)

References:

Statement: Cardiac safety

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Clinical cardiac tolerability of trastuzumab.

Perez EA, Rodeheffer R. J Clin Oncol. 2004 Jan 15;22(2):322-9. Review.

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Adjuvant Treatment with Trastuzumab: Schedules (13/14)

No further information

References:

Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831. M. Y. Halyard, T. M. Pisansky, L. J. Solin, L. B. Marks, L. J. Pierce, A. Dueck, E. A. Perez. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 523

Adjuvant Therapy with Other Targeted Agents (14/14)

Further information:

The BEATRICE-trial demonstrated no statistically significant improvement in invasive DFS with the addition of 1 year's bevacizumab to adjuvant chemotherapy for triple negative breast cancer (HR = 0.87 (95% CI: 0.72–1.07; p=0.1810) (Cameron 2012).

The BETH trial demonstrated no advantage of the addition of Bevacizumab to Platinum, Docetaxel and Trastuzumab in a large multicentre study with more than 3.000 patients, first presented at SABCS 2013.

References:

Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, Steger GG, Suter TM, Toi M, Parmar M, Laeufle R, Im YH, Romieu G, Harvey V, Lipatov O, Pienkowski T, Cottu P, Chan A, Im SA, Hall PS, Bubuteishvili-Pacaud L, Henschel V, Deurloo RJ, Pallaud C, Bell R. Lancet Oncol. 2013 Sep;14(10):933-42. doi: 10.1016/S1470-2045(13)70335-8. Epub 2013 Aug 7.

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Neoadjuvant (Primary) Systemic Therapy

Neoadjuvant Systemic Therapy

- **Version 2002:**
Costa
- **Versions 2003–2013:**
**Blohmer / Dall / Fersis / Göhring /
Harbeck / Heinrich / Huober / Jackisch /
Kaufmann / Lux / von Minckwitz / Müller /
Nitz / Schneeweiss / Schütz / Solomayer /
Untch**
- **Version 2014:**
Bauerfeind / Loibl

Subtype-specific General Systemic Strategies

AGO

➤ **HR+/HER2- and “low risk”:**

- Endocrine therapy without chemotherapy

++

➤ **HR+/HER2- and “high risk”**

- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated in case of high tumor burden
- Followed by endocrine therapy

++

+

++

➤ **HER2+**

- Trastuzumab plus
 - Sequential A/T-based regimen with concurrent T + H
 - Anthracycline-free, carboplatin-cont. regimen
 - Dose dense & escalated in case of high tumor burden

++

++

+

+

➤ **TNBC**

- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated

++

+

- In case of indication for chemotherapy, consider neoadjuvant approach

++

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|----|
| ➤ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy | 1a | A | |
| ➤ Pathological complete response is associated with improved survival in particular subgroups | 1b | A | |
| ➤ Can achieve operability in primary inoperable tumors | 1b | A | ++ |
| ➤ Improved options for breast conserving surgery | 1b | A | ++ |
| ➤ Allows individualization of therapy according to mid-course treatment effect | 1b | B | +* |

Neoadjuvant Systemic Chemotherapy Indications

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- **Inflammatory breast cancer**
- **Inoperable breast cancer**
- **Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation**
- **If similar postoperative adjuvant chemotherapy is indicated**
- **TNBC**
- **HER2 positive**

**Oxford / AGO
LoE / GR**

2b B ++

1c A ++

1b B +

1b A +

+

1b B +

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Neoadjuvant Systemic Chemotherapy Response Prediction I

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| Factor | CTS | LoE _{Ox2001} | GR | AGO |
|--|-----|-----------------------|----|-----|
| ➤ Young age | B | 1a | A | + |
| ➤ cT1 / cT2 tumors o. N0 o. G3 | B | 1a | A | ++ |
| ➤ Negative ER and PgR status | B | 1a | A | ++ |
| ➤ Triple negative breast cancer (TNBC) | B | 1a | A | ++ |
| ➤ Positive HER2 status | B | 1a | A | ++ |
| ➤ Non-lobular tumor type | B | 1a | A | + |
| ➤ Early clinical response | B | 1b | A | + |

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Neoadjuvant Systemic Chemotherapy Response Prediction II

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| Factor | LoE ₂₀₀₉ | CTS | GR | AGO |
|-----------------------------------|---------------------|-----|----|-----|
| ➤ PAM50/Mammaprint | III | C | B | +/- |
| ➤ Ki-67 | I | B | A | + |
| ➤ Tumour infiltrating Lymphocytes | II | B | B | + |
| ➤ <i>PIK3CA</i> mutation | II | B | B | + |

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

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- **Standard regimens used in the adjuvant setting with a duration of at least 18 weeks**

**Oxford / AGO
LoE / GR**

- **AC or EC → D q3w or P q1w**

1a A ++

- **DAC**

2b A ++

2b B ++

- **AP → CMF**

1b A +

- **Taxane followed by anthracycline sequence**

2b B +

- **Dose-dense regimen (e.g. E -P-CMF, E-P-C)**

1b B +*

- **Capecitabine in combination with anthracycline and taxane**

1b B +/-

- **Platinum in TNBC independent of BRCA-mutation**

2b B +*

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***Study participation recommended**

Possible Carboplatin Containing Regimen in the Neoadjuvant Setting

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| Author | Study | Regimen | pCR rate ypT0/is, ypN0 |
|-------------------------------------|-----------------------------|--|------------------------------|
| Positive studies | | | |
| Sikov et al. (SABCS 2013) | CALGB 40603 Phase III | Paclitaxel 80mg/m ² weekly x 12+Carboplatin AUC 6q3w x4 – dd AC (q2w) | 49% 60% (+Bev) |
| von Minckwitz et al. (ASCO 2013) | Phase II | NPLD20mg/m ² + Paclitaxel 80mg/m ² +Carboplatin AUC 1.5mg/m ² weekly x18 | 53% (+Bev) |
| Negative study | | | |
| Alba et al. BCRT 2013 | Phase II basal like | EC (90/600mg/m ²)q3w x4 – Docetaxel 75mg/m ² + Carboplatin AUC 6 q3w x 4 | 30% |

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Neoadjuvant Systemic Chemotherapy

Recommended Methods of Monitoring of Response

Oxford / AGO LoE / GR

| | | | |
|-----------------------------|-----------|----------|------------|
| ➤ Breast ultrasound | 2b | B | ++ |
| ➤ Palpation | 2b | B | ++ |
| ➤ Mammography | 2b | B | ++ |
| ➤ MRI | 2b | B | + |
| ➤ PET(-CT) | 1b | D | +/- |
| ➤ Clip tumour region | 5 | D | ++ |

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

Oxford / AGO LoE / GR

- | | | | |
|--|-----------|----------|------------|
| ➤ Trastuzumab in combination with chemotherapy | 1b | A | ++ |
| ➤ Lapatinib in combination with chemotherapy | 1b | B | - |
| ➤ Lapatinib + Trastuzumab in combination with chemotherapy | 2b | B | +/- |
| ➤ Pertuzumab + Trastuzumab in combination with chemotherapy | 2b | B | +* |
| ➤ Two anti-HER2 agents without chemotherapy | 2b | B | +/- |

* Study participation recommended

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Neoadjuvant Targeted Therapy in HER2 Negative Tumors

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LoE / GR**

Chemotherapy in combination with Bevacizumab

- In hormone receptor positive BC **2b B +/-**
- In TNBC **1b B +/-**

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Neoadjuvant Systemic Therapy Procedures in Case of Early Response

**Oxford / AGO
LoE / GR**

**In case of early response following
6 to 12 weeks of neoadjuvant
chemotherapy:**

➤ **Complete all chemotherapy before
surgery i.e. ≥ 18 weeks of treatment**

1b A ++

➤ **In case of response after 2 cycles of
DAC in HR positive breast cancer
consider 8 instead of 6 cycles of DAC**

2b C +

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Neoadjuvant Systemic Therapy Procedures in Case of No Early Response

Oxford / AGO
LoE / GR

In case of no change:

- **Completion of NST, followed by surgery**
- **Continuation of NST with non cross-resistant regimen**
 - **AC or EC x 4 → D x 4 or Pw x 12**
 - **DAC x 2 → NX x 4**

2b C ++

2b B +

2b B +

1b B +

In case of progressive disease:

- **Stop of NST and immediate surgery or radiotherapy**
- **Additional adjuvant chemotherapy with non cross-resistant regimen**

4 D ++*

4 D +/-*

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*** Study participation recommended**

Local/Regional Procedure after Neoadjuvant Therapy

**Oxford / AGO
LoE / GR**

- **Mark previous tumor region** **5 D ++**
- **Surgery** **2b C ++**
- **Microscopically clear margins** **5 D ++**
- **Tumor resection in the new margins** **3b C +**
- **Sentinel node biopsy**
(see chapter “Surgery”)

Surgical Procedure of the Axilla Before or After NACT

Oxford / AGO
LoE / GR

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SLNB before or after NACT in cN0

SLNB before NACT
SLNB after NACT

2b
3

B
B

+
+/-

Further surgical procedures depending on SLNB

| cN-Status (before NST) | pN-Status (before NST) | cN-Status (after NST) | Surgical procedure | | | |
|---------------------------|---------------------------------|--------------------------|-----------------------|---------|--------|----------|
| cN0 | pN0(sn) | - | nihil | 1a | A | + |
| cN0 | pN+(sn) analogue ACOG | ycN0 | ALND | 3 | B | +/- |
| cN0 | pN+(sn) not analogue ACOG | ycN0 | ALND | 2b | B | + |
| cN+ | cN+ (CNB/FNA) | ycN0 | SNB ALND | 3 2b | B B | +/- + |
| | | ycN+ (CNB/FNA) | ALND | 2b | B | ++ |

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Neoadjuvant Systemic Therapy

Indications for Mastectomy

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LoE / GR

- **Positive margins after repeated excisions** 3b C ++
- **Radiotherapy not feasible** 5 D ++
- **In case of clinical complete response**
 - **Inflammatory breast cancer** 2b C +
 - **In case of pCR** +/-
 - **Multicentric lesions** 3 C +/-
 - **cT4a-c breast cancer** 2b B +/-

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Neoadjuvant Systemic Therapy

Timing of Surgery and Radiotherapy

Oxford / AGO
LoE / GR

➤ Surgery

4 C ++

- After the nadir of the leucocyte count
(2 to 4 weeks after last course of
chemotherapy)

➤ Radiotherapy after surgery

2b B ++

2–3 weeks after surgery BCS

Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

**Oxford / AGO
LoE / GR**

- **Endocrine treatment in
endocrine responsive disease**
- **Complete trastuzumab treatment
for 1 year in HER2-positive
disease**
- **In case of insufficient response**
 - **Further chemotherapy**
 - **Experimental therapies in clinical trials**

1a A ++

2b B ++

3 C -

5 D +

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Neoadjuvant Endocrine Therapy

- **Postmenopausal patients with endocrine-responsive breast cancers who are inoperable and can / will not receive chemotherapy**
- **Optimizes the option for breast conserving therapy in postmenopausal patients with endocrine-responsive tumors**
- **Aromatase inhibitors (for > 3 months)**
- **Premenopausal patients with endocrine-responsive breast cancers who are inoperable and can / will not receive chemotherapy**
 - **Tamoxifen**
 - **Aromatase inhibitors+ LHRH**
- **Concurrent chemo-endocrine therapy**
- **Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status**

Oxford / AGO LoE / GR

| 2a | B | + |
|----|---|-----|
| 1b | A | + |
| 1b | B | + |
| | | + |
| 2b | C | + |
| 1b | C | +/- |
| 1b | A | - |
| 1b | B | + |

Optimal duration of neoadjuvant endocrine therapy is unknown

No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

Neoadjuvant (Primary) Systemic Therapy (2/20 and 3/20)

Further information:

Systematic review of published evidence:

PUBMED 1999-2012

ASCO 1999-2012

SABCS 1999-2012

ECCO/ESMO 1999-2012

Systematic review of national and international guidelines: St. Gallen, NIH, ASCO, German guidelines

References:

Selected review articles:

1. Kaufmann M, et al. Ann Oncol 18, 1927, 2007
2. Goldhirsch A, et al. Ann Oncol 20, 1319, 2009
3. Goldhirsch A, et al. Ann Oncol 22, 1736, 2011
4. Makhoul I, et al. J Surg Oncol 103, 348, 2011
5. Kaufmann M, et al. Ann Surg Oncol 19, 1508, 2012

Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information:

Survival rates are similar after primary systemic (preoperative, neoadjuvant) therapy (NST) and adjuvant therapy.¹⁻⁴ Pathological complete response (pCR) is associated with improved survival.⁴⁻⁸ In retrospective analyses of the German patient cohorts, this treatment effect is confined to specific subgroups in particular to patients with triple negative, HER2+ (non-luminal) and luminal B (HER2 negative) breast cancer.^{8,9} Achievement of pCR according to the most strict definition of no invasive and no non-invasive tumor residues in the breast and axilla (ypT0 ypN0) predicts the most favorable overall survival.^{7, 8}

Advantages of NST are

- (1) improved operability of primary inoperable tumors,¹⁰
- (2) higher rate of breast conserving surgery,¹⁰
- (3) selection of individualized therapy by early identification of treatment failures,⁸
- (4) evaluation of short-term surrogate markers (clinical, pathologic, molecular) to predict long-term outcome,⁸ and
- (5) rapid evaluation of new drugs or treatment modalities.¹¹

Disadvantage of NST is

- (1) In one metaanalysis from 2005 an increased rate of loco-regional recurrences was suggested. However, this metaanalysis included trials where surgery was withheld in numerous patients.¹²

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Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information:

Neoadjuvant systemic therapy (NST) is indicated in inoperable and inflammatory breast cancer, but also in operable breast cancer with tumor diameters of at least 2 centimeters.¹⁻³ NST is a valid treatment option, if mastectomy seems necessary, but patient wishes breast conservation,^{3,4} and for all patient who would need adjuvant chemotherapy after adequate evaluation of radiological, histological and clinical prognostic factors.⁵ Patients may choose to receive systemic therapy before surgery to take advantage of the response assessment of the primary tumor as tumor response to NST is a surrogate for the effect of chemotherapy on micrometastases.⁶ Furthermore, a demonstrable response to NST may have a positive effect on patients compliance. NST may also be an option for patients who wish to delay surgery, eg. in the second or third trimester of pregnancy.⁷

It is especially indicated in TNBC and HER2+ breast cancer, because pCR correlates very well with the outcome in these subtypes.^{8,9}

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Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)

Further information:

According to a metaanalysis including 3332 patients treated in 7 German neoadjuvant trials clinico-pathological factors predicting pCR following NST are younger age, smaller tumor size, non-lobular histology, higher grade, negative hormone receptor (HR) status, triple negative and HER2 positive status.^{1,2} Considering subgroups higher probability of pCR was associated with longer treatment in HR positive tumors, higher anthracycline doses in HR negative tumors, short-term higher-dose taxane- and anthracycline-based treatment in triple negative tumors, trastuzumab-containing treatment in HER2 positive tumors and the addition of capecitabine in all subtypes.¹

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Neoadjuvant Systemic chemotherapy - Response Predictiong II (7/20)

Further information:

Further predictive parameters are the presence of tumor-associated lymphocytes, and other proliferation marker like Ki-67 and topoisomerase II α .¹⁻⁴ The assessment of Ki-67 before therapy has prognostic and predictive impact.^{5,6} Although results of several gene expression profiling studies are promising, at the moment, none of these signatures has been proven to be of sufficient discriminatory power to be used in clinical setting.⁷

It has been shown that TNBC subclassified by the Vanderbilt/Lehman signature into 7 subtypes has predictive information.⁸ It was previously shown that the androgen receptor positive TNBC have a lower rate of achieving a pCR.⁹ The luminal AR subtype is one of the 7 classified by Lehmann.

In HER2 positive breast cancer, the absolute amount of ER seems to play a role in predicting response to neoadjuvant therapy.¹⁰

The *PIK3CA* mutated HER2+ tumours achieve a significantly lower pCR rate than the wild-type tumours.¹¹⁻¹³ Especially in patients receiving a dual anti-HER2 treatment.

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)

Further information:

Outside clinical trials the same regimens should be used for NST as in the adjuvant setting ie. anthracyclines and taxanes concurrently or sequentially for at least 6 cycles (18 weeks) or 6 months, respectively.¹ Trastuzumab should be provided to all patients with HER2 overexpressing breast cancer and no cardiac comorbidity.^{2,3} Recommended regimens are those used in the superior treatment arms of large randomized trials (NSABP B-27,⁴ GeparDuo,⁵ GeparTrio,^{6,7} ECTO⁸).

A short dose-dense chemotherapy regimen with epirubicin and paclitaxel increased pCR rate and survival as compared to four cycles of standard dose epirubicin plus paclitaxel.⁹ A sufficiently long NST with dose intensified epirubicin and paclitaxel followed by CMF, however, increased only pCR rate but not DFS as compared to standard treatment.^{10,11} Nevertheless analogue to the adjuvant setting, the use of a standard dose intensified regimen as neoadjuvant treatment should be considered if the patients would most probably receive this regimen in the adjuvant setting. Several regimen from the adjuvant setting and the neoadjuvant setting can be used.

Several studies have examined the use of capecitabine in the neoadjuvant setting with conflicting results.¹²⁻¹⁴ One metaanalysis of the German neoadjuvant trials point to the fact that capecitabine might play a role in NST but further prospective trials are needed.¹⁵

Platinum salts, have recently been shown in large prospectively randomized trials (the German GeparSixto study and the American CALGB 40603 study^{16,17} to increase pCR rates when given as part of the neoadjuvant chemotherapy, supporting the previous data from mainly small, non-randomized trials¹⁸⁻²¹. The study from Alba et al. combining Carboplatin with docetaxel (75mg/m²) compared to docetaxel 100mg/m² could not demonstrate superiority for the carboplatin arm. However, it has not been shown that this is specific platinum effect and not merely the effect of an alkylating agent.

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Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information:

Monitoring during treatment must include breast examination before each cycle. The frequency and nature of imaging assessment during chemotherapy is controversial. Minimal requirements for the surgeon include clinical examination, mammogram, ultrasound, and in selected cases MRI.¹ The response measured by breast ultrasound after 2 cycles of NST is a good predictor of later pCR.^{2,3} Various studies describe a good prediction of pCR if the breast MRI shows a good response in size of the tumor and reduction in volume and in contrast agent dynamic.⁴ However, the accuracy of MRI is not adequate to obviate either the need for staging by sentinel node biopsy or the need for complete axillary dissection in women determined to be node positive prior to NST.⁵ FDG-PET does not provide an accurate assessment of residual tumour after primary chemotherapy of breast cancer and is therefore not recommended outside clinical trials.⁶

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information:

Several studies have examined the use of trastuzumab in combination with chemotherapy for patients with HER2 positive breast cancer in the neoadjuvant setting.¹⁻⁶ The results of randomized trials demonstrated that, compared to chemotherapy alone, neoadjuvant trastuzumab plus chemotherapy significantly increased pathologic complete response rate.¹⁻⁵ Improvements in disease-free, event-free and overall survival were also reported.¹⁻³ The achievement of pCR with chemotherapy and trastuzumab was associated with improved disease-free survival, distant disease-free survival and overall survival.^{2,3,6-9}

The use of lapatinib instead of trastuzumab can not be recommended, although efficacy can be seen in HER2 positive tumors.^{10,11}

The combination of chemotherapy with trastuzumab and lapatinib or pertuzumab can significantly increase the pathologic complete response rate, but should preferably be used in clinical studies in the neoadjuvant setting until further results are available, although the combination of trastuzumab and pertuzumab has been licensed by the FDA for neoadjuvant therapy.¹¹⁻¹⁴ Chemotherapy-free regimens combining 2 anti-HER2 agents were also active.^{15,16}

Subcutaneous trastuzumab, has a pharmacokinetic profile and efficacy non-inferior to standard intravenous administration, and therefore offers a valid treatment alternative.¹⁷

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Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)

Further information:

Three large randomized phase III studies showed a higher pCR rate after combination of chemotherapy and bevacizumab than with chemotherapy alone in patients with HER2 negative breast cancer in the neoadjuvant setting. In the German GeparQuinto trial, while no effect of bevacizumab was seen in hormone receptor (HR) positive patients,¹ bevacizumab significantly increased the pCR rate in the triple negative subgroup.^{1,2} In the NSABP B40 trial, however, the effect of bevacizumab was seen predominantly in HR positive breast cancer.³ This controversial results cannot be explained for now. The CALGB study is the 3rd trial showing an increased pCR by adding bevacizumab to chemotherapy.⁴ Long term data need to be awaited before the recommendation for neoadjuvant bevacizumab can be granted.

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Neoadjuvant Systemic Therapy Procedures in Case of Early Response (13/20)

Further information:

Early response following 2 to 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound is associated with higher pCR rates at surgery.¹⁻³ In case of early response NST should be completed as planned.⁴ In patients responding to 2 cycles of TAC, however, continuation of treatment with additional 6 instead of 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective, unplanned subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer.⁵

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Neoadjuvant Systemic Therapy Procedures in Case of No Early Response (14/20)

Further information:

In case of no change following 2 to 4 cycles (6 to 12 weeks) of an anthracycline-containing NST as assessed by clinical examination or ultrasound alternative strategies should be discussed. Completion of NST as planned is associated with a clinical response in around 50% of patients. The pCR rate, however, is only 2-6%.^{1,2} Following 4 cycles of an anthracycline-containing regimen the switch to taxanes is recommended.³ Survival in an unselected group of patients, however, is not improved.⁴ The addition of everolimus to paclitaxel is not justified.⁵ In case of no response following 2 cycles of TAC, however, the switch to 4 cycles of vinorelbine plus capecitabine (NX) instead of continuation with 4 cycles of TAC significantly improved disease-free and overall survival. In a retrospective subgroup analysis this benefit was confined to patients with hormone receptor positive breast cancer.⁶

In case of progressive disease immediate surgery or primary radiotherapy is recommended.⁷ Patients who have extensive residual cancer after a full course anthracycline and taxane containing NST remain at high risk for relapse, in particular patients with grade 3 and hormone receptor negative breast cancer.⁸ Those patients should be referred to participation in postneoadjuvant clinical trials.⁷

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Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

Further information:

Precise documentation of tumor location before, during and at the end of NST is necessary. Surgery is an integral part of primary breast cancer treatment following NST. The aim of surgery is to completely remove invasive and non invasive breast cancer residues after NST and to obtain clear margins at pathology examination. No compromise should be made in surgical margins to obtain better cosmetic results. Under these circumstances excision within new tumor margins might be feasible according to current data. Thus far, studies evaluating sentinel node biopsy after NST have been inconsistent with regard to feasibility and efficacy. Therefore, it is not recommended outside of clinical trials, see also chapter surgery.¹⁻⁴

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Neoadjuvant Systemic Therapy - Indications for Mastectomy (17/20)

Further information:

Breast conserving surgery (BCS) should not be considered if negative margins are not achievable even after repetitive excisions, in case of widespread DCIS or microcalcifications, in case of inflammatory breast cancer or if adjuvant radiotherapy is not feasible.¹⁻³ In cases with cT4a-c tumors or multicentric lesions (lesions in different quadrant) BCS is also not recommended.¹⁻⁵ However, if a clinical complete response is achieved following NST, BCS should be evaluated within controlled clinical trials.

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Neoadjuvant Systemic - Therapy Timing of Surgery and Radiotherapy (18/20)

Further information:

It is unknown whether preoperative radiotherapy following NST achieved similar results as radiotherapy following NST and surgery. Preoperative radiotherapy might result in higher rates of breast conservation without compromising cosmetic result.¹ However, preoperative external beam and brachytherapy are not established as modes of treatment in conjunction with NST² and do not replace adequate surgery³⁻⁶ which should be performed after leucocyte nadir around 2 to 4 weeks following last cycle of chemotherapy.⁷ Adjuvant radiotherapy after NST should be administered according to the same recommendations made for those patients who do not receive NST. Even in patients with pCR following NST whole breast irradiation is indicated after breast-conserving surgery.^{3,4} If surgery can be omitted after pCR has still be to confirmed.^{7,8}

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Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment (19/20)

Further information:

Postneoadjuvant therapy is indicated in patients at high risk of relapse after neoadjuvant therapy.¹ The NATAN study using a bisphosphonate in unselected women with residual cancer was not successful.² Currently several trials have started investigating palbociclib in patients at very high risk after neoadjuvant therapy with luminal type breast cancer.³ The Katherine study investigates the use of T-DM1 instead of trastuzumab after PST.⁴

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Neoadjuvant Endocrine Therapy (20/20)

Further information:

NST with aromatase inhibitor represents an option for postmenopausal patients with highly endocrine responsive breast cancer, which can improve breast conservation rate.¹⁻⁵ However, chemotherapy is still widely used in this setting despite small studies showing little advantage over an endocrine approach.³ The lack of a practice standard reflects the absence of a phase III trial definitively comparing neoadjuvant endocrine therapy with neoadjuvant chemotherapy. Neoadjuvant endocrine therapy might be reasonable for postmenopausal patients with hormone receptor positive breast cancer who are inoperable and for whom it is desirable to avoid certain chemotherapy related adverse events. According to prospective data from randomized trials and systemic review, aromatase inhibitors are more active and better tolerated than tamoxifen.^{1,2,5} All 3 third generation aromatase inhibitors have similar activity.⁶ Current data support a duration of at least 3 months, but do not support the use of concurrent preoperative chemotherapy.^{5,7} The achievement of pCR is not a suitable surrogate endpoint for survival in luminal A type and HER2+ luminal B type breast cancer.⁸ Patients with pathologically node-negative T1 or T2 disease with a fully suppressed Ki67 level and persistent estrogen receptor expression after completion of NST have a very low risk of relapse.⁹ A small study in premenopausal women comparing ARI plus GnRH with Tam + GnRH demonstrate a superiority for the ARI.¹⁰

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Preliminary Note

- **The recommendations of the AGO differ in a few statements from those of the Societies of the Radiooncologists (DEGRO and ARO).**
- **AGO and Radiooncologic Societies are working on a common statement.**

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Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

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| | | | |
|---|----|---|-----|
| ➤ > 3 tumor infiltrated lymph nodes (Lnn.) | 1a | A | ++ |
| ➤ 1–3 tumor infiltrated lymph nodes (Lnn.) (depending on patient's age) | 1a | A | + |
| ➤ T3 / T4 | 1a | A | ++ |
| ➤ pT3 pN0 R0 (and no additional risk factors) | 2b | B | +/- |
| ➤ If R0 is impossible to reach (for invasive tumor) | 1a | A | + |
| ➤ After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d) | 2a | A | + |
| ➤ In young pts with high risk features | 2b | C | ++ |
| ➤ Omission of radiotherapy in case of ypT0 ypN0 after NACT | 3b | C | +/- |
| ➤ Additional RT of supra- /infraclav. region in >3+Lnn | 1a | A | ++ |
| ➤ Additional RT of regional lymphatics (i.e. parasternal Lnn.) in high risk/pN0 or pN1-3 | 2a | B | +/- |
| * Indications for PMRT and regional RT are independent of adjuvant systemic treatment | 1a | A | ++ |

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RT of the Breast after Breast Conserving Surgery (BCS) in Invasive Carcinoma

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LoE / GR

➤ Whole breast irradiation (WBI)

- Standard fractionation
- Hypofractionation for WBI (+/- sequential boost)

➤ Boost-irradiation (improves local control)

- Absolute benefit depending on patient's age
- Dose-effect relationship independent of pts.' age

➤ Boost-irradiation in node-negative tumors, endocrine responsive, complete resection

➤ Intraoperative irradiation (IORT/IOERT)

- As boost-irradiation followed by WBI
- As sole radiotherapy modality
 - IORT using 50 kV (pT1, N0, G1-2, non-lobular cancer, age >50 y, R0, no extensive DCIS, IORT during first surgery, HR+)
 - IOERT

➤ Brachytherapy as sole radiotherapy modality

- Interstitial brachytherapy
- Intracavity balloon technique

| | | |
|----|---|------|
| 1a | A | ++ |
| 1a | A | +° |
| 1a | A | ++° |
| 1a | A | + |
| 1b | | |
| 1b | | |
| 3a | C | +/- |
| 2a | B | + |
| 1b | B | +* |
| 1b | B | -* |
| 1b | B | +/-* |
| 1b | C | -* |

° GR is dissent from the updated DEGRO practical guidelines 2013/14

* Study participation recommended

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Boost RT after BCS in Invasive Carcinoma

Oxford / AGO LoE / GR

➤ Improved local tumor control

- All ages: LRR reduction (7–12%)
- < 40 years: LRR reduction (10–29%)
- High grade invasive ductal cancer

➤ Additional boost RT does not impact survival (10-years data)

➤ No worsened adverse effects in hypofractionated WBI if boost is given sequentially after WBI

➤ Hypofractionated WBI + sequential boost

➤ Hypofractionated WBI + simultaneously integrated boost

➤ Normofractionated WBI + simultaneously integrated boost

➤ Intraoperative boost + hypofractionated WBI

| | | |
|----|---|----|
| 1b | A | + |
| 1b | A | + |
| 1b | A | ++ |
| 2b | A | + |

| | | |
|----|---|------|
| 1b | B | + |
| 2b | C | +/-* |
| 1b | B | + |
| 5 | D | -* |

* Study participation recommended

Radiotherapy of the Axilla

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|------------|
| ➤ Tumor residuals after axillary dissection | 2b | B | ++ |
| ➤ Sentinel node negative | 1 | B | -- |
| ➤ Axillary dissection not indicated (e.g. SLN positive, see surgical chapter) | 2a | B | - |
| ➤ Extracapsular tumor spread (ECS) | 2b | B | -- |
| ➤ Axillary micrometastases or isolated cells found in regional lymph nodes | 3b | B | -- |
| ➤ Instead of axillary lymph node dissection if SNB is positive^o | 1 | B | +/- |

^o AMAROS trial

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas

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Supra-/infraclavicular lymphatics irradiation:

- Level III involved
- In case of irradiation of axilla
- pN1a
- pN2a
- (p)N3a-c
- After NACT/NAT (if pretreatment nodal status was clinically positive)*

Axillary irradiation

- Following axillary clearing of level I + II
- SNB -
- In case of contraindication or patients withdrawal of sufficient axillary clearing

Internal mammae lymph node irradiation

The respective contribution of RNI by site (SCN vs. IMN) on improved outcome cannot be distinguished

**Oxford / AGO
LoE / GR**

| | | |
|-----------------|---|-----|
| 1 | B | + |
| 3b | B | + |
| 1 | A | +/- |
| 1 | A | ++ |
| 1 | A | ++ |
| 3 | C | +/- |
| 3b | D | - |
| 4 | D | - |
| 2a ^a | B | +/- |
| 1 | B | +/- |

*consider risk / benefit relationship of RT

^aAMAROS trial

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References

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HEILEN

Radiotherapy of Other Locoregional Lymph Node Areas

Oxford / AGO
LoE / GR

➤ Internal mammary lymph node irradiation*:

➤ N2b, N3b

➤ \geq pN1b (involvement of internal mammary lymph node detected by SNB)

➤ pN1c–pN3

➤ medial / central tumor, pN0 +/- risk factors

1 B +/-

1 B +/-

1 B +/-

*RT of internal mammary lymphatics may provide benefits (OS, DMFS, LRR) in recently published RCTs and a meta-analysis

Concomitant Use of Systemic Therapy with Radiotherapy

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- **Trastuzumab concurrent with radiotherapy**
- **Tamoxifen concurrent with radiotherapy**
- **AI (Letrozol) concurrent with radiotherapy**

**Oxford / AGO
LoE / GR**

2b B +

3b C +

2a B +/-

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Radiotherapy in the Elderly Patient

Oxford / AGO
LoE / GR

Omission of radiotherapy in *low risk patient if
adjuvant endocrine treatment (Tam, 5-yrs) takes place**

1b A +

Increase in local recurrence, no influence on OS, decrease in toxicity

*** ≥ 70 year of age, pT1, pN0, HR positive, G1-2,
HER2-negative, negative resection margin width >1 mm**

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Further
Information

References

Adjuvant Radiotherapy (2/11)

Further information and references:

Update January 2014 – Souchon, Blohmer

Screened data bases: Pubmed 2013-January 2014; SABCS 2012-2013; ASCO 2012-2013, ASTRO 2012-2013, ESTRO 2012-2013; Cochrane Database Syst Rev 2013

Screened guidelines: NCCN – Clinical Practice Guidelines in Oncology – Breast cancer: V.3.2013; DEGRO 2013-January 2014; International Society Geriatric Oncology; Consensus on the primary therapy of early breast cancer (St. Gallen 2013); S3-Guideline of the German Cancer Society 2012; NICE (UK) Clinical Guidelines 2009-2013; Guidelines for clinical practice from French expert review board of Nice/Saint-Paul de Vence; French national guidelines 2011/2012; National Cancer Institute (USA) 2013; Scottish Intercollegiate Guidelines Network (SIGN) 2013; New Zealand Guidelines Group (NZGG) 2009-2010; National Health and Medical Research Council (NHMRC Australia) 2013; Belgian Health Care Knowledge Centre (KCE) 2013; Guidelines International Network (G-I-N) 2013; British Medical Journal (BMJ) clinical guidelines (2009-2013); International Society of Geriatric Oncology (SIOG), European Society of Medical Oncology (ESMO) and European Society of Breast Cancer Specialists (EUSOMA) 2013.

MAIN TOPICS:

New in 2013:

I. New or updated guidelines 2013 / recommendations mostly regarding evidence based medicine criteria 2013

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38

Danish Breast Cancer Cooperative Group Radiotherapy Committee. Nielsen MH, Berg M, Pedersen AN, et al; Danish Breast Cancer Cooperative Group Radiotherapy Committee. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol 2013;52:703-10

DEGRO Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Is the simultaneously integrated boost (SIB) technique for

early breast cancer ready to be adopted for routine adjuvant radiotherapy? Statement of the German and the Austrian Societies of Radiooncology (DEGRO / ÖGRO). *Strahlenther Onkol* 2013;189:193-196

DEGRO Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I: Radiotherapy following breast conserving therapy for invasive breast cancer. *Strahlenther Onkol* 2013;189:825-833

DEGRO Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Souchon R, Sautter-Bihl M-L, Sedlmayer F, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer II - Radiotherapy of non-invasive neoplasia of the breast. *Strahlenther Onkol* 2014;190:8-16

DEGRO Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Sautter-Bihl ML, Sedlmayer F, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III: - Radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014;190: in press

European Society of Breast Cancer Specialists. Cardoso F, Loibl S, Pagni O, et al.; The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29.

European Society of Medical Oncology (ESMO): Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Senkus E, Kyriakidis S, Penault-Llorca F, et al. *Ann Oncol* 2013, Oct;24 Suppl 6:vi7-23. doi: 10.1093/annonc/mdt284. Epub 2013 Aug 22

Fontein DBY, van de Water W, Mieog JSD, et al. Timing of the sentinel lymph node biopsy in breast cancer patients receiving neoadjuvant therapy – Recommendations for clinical guidance. *EJSO* 2013;39:417-424

Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer. *Ann Oncol* 2013;24:2206-2223

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National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013.
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. JNCCN 2013;11:753-761

National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134)

Ia. Unchanged guidelines 2013 / recommendations 2013

a) Mammacarcinoom. Landelijke richtlijn, Versie: 2.0. Datum Goedkeuring: 13-02-2012. Richtlijn Mammacarcinoom. Evidenced-based Guideline 13.02.2012: www.oncoline.nl/mammacarcinoom.

b) Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. 3. Auflage: Aktualisierung 2012. Zuckschwerdt Verlag, 2012 ISBN: 978-3-86371-073-6

c) Besnard S, Cutuli B, Fourquet A, et al. Radiothérapie du cancer du sein infiltrant: recommandations nationales françaises [Radiotherapy of invasive breast cancer: French national guidelines] Cancer Radiother 2012;16:503-513 French.

Cutuli B. [Radiotherapy for breast cancer: Which strategy in 2012?]. Cancer Radiother 2012;16:493-502

e) Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012;13:e148-60

Unchanged guidelines (regarding radiooncological issues): In 2013 no update and/or changed guideline recommendations, respectively, regarding RT in primary treatment of breast cancer:

American Society of Clinical Oncology (ASCO); National Health and Medical Research Council (NHMRC Australia)

Unchanged: National Institute for Health and Clinical Excellence UK– (NICE UK) Guidelines (2009): 2012: no update

Unchanged: updated New Zealand Guidelines Group (NZGG) 2009-2010: New Zealand Guidelines Group. Management of early breast cancer. Wellington: New Zealand Guidelines Group; 2009. or www.nzgg.org.nz

II New overviews / (updated) metaanalyses / systematic reviews:

New in 2013:

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. Radiat Oncol 2013; 8:267

- Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-98. doi: 10.1056/NEJMoA1209825.
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- Goyal A, Duley L, Fakis A. Axillary treatment for patients with early breast cancer and lymph node metastasis: systematic review protocol. *World J Surg Oncol* 2013;11:6. doi: 10.1186/1477-7819-11-6. Review.
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- Shah C, Kundu N, Arthur D, Vicini F. Radiation therapy following postmastectomy reconstruction: a systematic review. *Ann Surg Oncol* 2013;20:1313-1322.
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van de Water W, Bastiaannet E, Scholten AN, et al. Breast-Conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: A systematic review and meta-analysis. *Ann Surg Oncol* 2013 Nov 23. [Epub ahead of print]

Wang J, Xie X, Wang X, Tang J, et al. Locoregional and distant recurrences after breast conserving therapy in patients with triple-negative breast cancer: A meta-analysis. *Surg Oncol* 2013;22:247-55. doi: 10.1016/j.suronc.2013.10.001. Epub 2013 Oct 12.

Yang TJ, Tao R, Elkhuzien PH, van Vliet-Vroegindewey C, Li G, Powell SN. Tumor bed delineation for external beam accelerated partial breast irradiation: A systematic review. *Radiother Oncol* 2013;108:181-9. doi: 10.1016/j.radonc.2013.05.028. Epub 2013 Jun 24.

Zhang P-Z, Chong L, Zhao Y, Gu J, Tian J-H, Yang K-H. Is axillary dissection necessary for breast cancer in old women? A meta-analysis of randomized clinical trials. *Asian Pacific J Cancer Prev* 2013;14:947-950

Zhou Y, Zhou W, Liu Q, et al. XRCC1 R399Q polymorphism and risk of normal tissue injury after radiotherapy in breast cancer patients. *Tumour Biol* 2013 Dec 3. [Epub ahead of print]

Ila: New overview / metaanalysis / systematic reviews regarding DCIS in 2013:

Updated Meta-analysis:

Goodwin A, Parker S, Ghera D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. *Cochrane Database Syst Rev*. 2013 Nov 21;11:CD000563. doi: 10.1002/14651858.CD000563.pub7.

OBJECTIVES:

To summarise the data from RCTs testing the addition of RT to BCS for treatment of DCIS to determine the balance between the benefits and harms.

SEARCH METHODS:

We searched the Cochrane Breast Cancer Group Specialised Register (2 June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, Issue 1), MEDLINE (2 June 2011), EMBASE (2 June 2011) and the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP; 2 June 2011). Reference lists of articles and handsearching of ASCO (2007), ESMO (2002 to 2007), and St Gallen (2005 to 2007) conferences were performed.

SELECTION CRITERIA:

RCTs of breast conserving surgery with and without radiotherapy in women at first diagnosis of pure ductal carcinoma in situ (no invasive disease present).

MAIN RESULTS:

Four RCTs involving 3925 women were identified and included in this review. All were high quality with minimal risk of bias. Three trials compared the addition of RT to BCS. One trial was a two by two factorial design comparing the use of RT and tamoxifen, each separately or together, in which participants were randomised in at least one arm. Analysis confirmed a statistically significant benefit from the addition of radiotherapy on all ipsilateral breast events (hazards ratio (HR) 0.49; 95% CI 0.41 to 0.58, $P < 0.00001$), ipsilateral invasive recurrence (HR 0.50; 95% CI 0.32 to 0.76, $p=0.001$) and ipsilateral DCIS recurrence (HR 0.61; 95% CI 0.39 to 0.95, $P = 0.03$). All the subgroups analysed benefited from addition of radiotherapy. No significant long-term toxicity from radiotherapy was found. No information about short-term toxicity from radiotherapy or quality of life data were reported.

AUTHORS' CONCLUSIONS:

This review confirms the benefit of adding radiotherapy to breast conserving surgery for the treatment of all women diagnosed with DCIS. No long-term toxicity from use of radiotherapy was identified.

Further references regarding DCIS published in 2013:

Abbott AM, Portschi PR, Lee C, et al. Prospective multicenter trial evaluating balloon-catheter partial-breast irradiation for ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys* 2013;87:494-8. doi: 10.1016/j.ijrobp.2013.06.2056.

CONCLUSIONS: Accelerated partial-breast irradiation using MammoSite seems to provide a safe and cosmetically acceptable outcome; however, the 9.8% IBTR rate with median follow-up of 5.3 years is concerning. Prospective randomized trials are necessary before routine use of APBI for DCIS can be recommended.

Benson JR, Wishart GC. Predictors of recurrence for ductal carcinoma in situ after breast-conserving surgery. *Lancet Oncol* 2013;14:e348-57. doi: 10.1016/S1470-2045(13)70135-9. Review.

Boxer MM, Delaney GP, Chua BH. A review of the management of ductal carcinoma in situ following breast conserving surgery. *Breast* 2013;22:1019-25. doi: 10.1016/j.breast.2013.08.012. Epub 2013 Sep 23.

Donker M, Litière S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III Trial. *J Clin Oncol* 2013;31:4054-9. doi: 10.1200/JCO.2013.49.5077.

CONCLUSION:

At 15 years, almost one in three nonirradiated women developed an LR after LE for DCIS. RT reduced this risk by a factor of 2. Although women who developed an invasive recurrence had worse survival, the long-term prognosis was good and independent of the given treatment.

Fitzsullivan E, Lari SA, Smith B, et al. Incidence and consequence of close margins in patients with ductal carcinoma-in situ treated with mastectomy: is further therapy warranted? *Ann Surg Oncol* 2013;20:4103-12. doi: 10.1245/s10434-013-3194-0

BACKGROUND:

The impact of close margins in patients with ductal carcinoma-in situ (DCIS) treated with mastectomy is unclear; however, this finding may lead to a recommendation for postmastectomy radiotherapy (PMRT). We sought to determine the incidence and consequences of close margins in patients with DCIS treated with mastectomy.

RESULTS:

Overall, 94 patients (11.7 %) had close margins (positive, n = 5; negative but ≤ 1 mm, n = 54; 1.1-2.9 mm, n = 35). Independent risk factors for close margins included multicentricity, pathologic lesion size ≥ 1.5 cm, and necrosis, but not age, use of skin-sparing mastectomy, or immediate reconstruction (p > 0.05). Seven patients received PMRT, and none had a locoregional recurrence (LRR). Among the remaining 803 patients, the 10-year LRR rate was 1 % (5.0 % for margins ≤ 1 mm, 3.6 % for margins 1.1-2.9 mm, and 0.7 % for margins ≥ 3 mm [p < 0.001]). The 10-year rate of contralateral breast cancer was 6.4 %. On multivariate analysis, close margins was the only independent predictor of LRR (p = 0.005).

CONCLUSIONS:

Close margins occur in a minority of patients undergoing mastectomy for DCIS and is the only independent risk factor for LRR. As the LRR rate in patients with close margins is low and less than the rate of contralateral breast cancer, PMRT is not warranted except for patients with multiple close/positive margins that cannot be surgically excised.

Guenzi M, Giannelli F, Bosetti D, et al. Two different hypofractionated breast radiotherapy schedules for 113 patients with ductal carcinoma in situ: preliminary results. *Anticancer Res* 2013;33:3503-7.

Rakovitch E, Narod SA, Nofech-Moses S, et al. Impact of boost radiation in the treatment of ductal carcinoma in situ: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2013;86:491-7.

Rakovitch E, Nofech-Moses S, Narod SA, et al. Can we select individuals with low risk ductal carcinoma in situ (DCIS)? A population-based outcomes analysis. *Breast Cancer Res Treat* 2013;138:581-90.

Skandarajah AR, Bruce Mann G. Selective use of whole breast radiotherapy after breast conserving surgery for invasive breast cancer and DCIS. *Surgeon* 2013;11:278-85.

Three meta-analyses and 17 randomised controlled trials have been published in invasive disease and one meta-analysis and four randomised controlled trials for DCIS. Overall, adjuvant radiotherapy provides a 15.7% decrease in local recurrence and 3.8% decrease in 15-year risk of breast cancer death. The key clinico-pathological factors, which enable stratification into high, intermediate or low risk groups include age, oestrogen receptor positivity, use of tamoxifen and extent of surgery. Absolute reductions in 15-year risk of breast cancer death in these three prediction categories are 7.8%, 1.1%, and 0.1% respectively. Adjuvant radiotherapy provides a 60% risk reduction in local recurrence in DCIS with no impact on distal metastases or overall survival. Size, pathological subtype and margins are major risk factors for local recurrence in DCIS.

Soeteman DI, Stout NK, Ozanne EM, et al. Modeling the effectiveness of initial management strategies for ductal carcinoma in situ. J Natl Cancer Inst 2013;105:774-81. doi: 10.1093/jnci/djt096. Epub 2013 May 3.

Comment in: Informing patient decisions regarding management of ductal carcinoma in situ. [J Natl Cancer Inst. 2013]

Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. J Natl Cancer Inst 2013;105:701-10.

Conclusions The DCIS Score quantifies IBE risk and invasive IBE risk, complements traditional clinical and pathologic factors, and provides a new clinical tool to improve selecting individualized treatment for women with DCIS who meet the ECOG E5194 criteria.

Souchon R, Sautter-Bihl M-L, Sedlmayer F, et al. DEGRO practical guidelines: radiotherapy of breast cancer II - Radiotherapy of non-invasive neoplasia of the breast. Strahlenther Onkol 2014;190:8-16

Vicini FA, Shaitelman S, Wilkinson JB, et al. Long-term impact of young age at diagnosis on treatment outcome and patterns of failure in patients with ductal carcinoma in situ treated with breast-conserving therapy. Breast J 2013;19:365-73. doi: 10.1111/tbj.12127.

White J. Do we need to irradiate all small invasive breast cancers and DCIS? Am Soc Clin Oncol Educ Book. 2013:40-4. doi: E10.1200/EdBook_AM.2013.33.40.

Special aspect: PMRT in patients with DCIS if R0 is impossible to reach

Childs SK, Chen YH, Duggan MM, et al. Impact of margin status on local recurrence after mastectomy for ductal carcinoma in situ. Int J Radiat Oncol Biol Phys 2013;85:948-52

I**II**b) *invasive breast cancer*

1. *The impact of age on outcome in early-stage breast cancer*

New in 2013:

Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on clinical management of the axilla in older breast cancer patients: A SEER-Medicare analysis. Ann Surg Oncol 2013;20:4145-52 .

Hwang ES, Lichtensztajn DY, et al. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer 2013;119:1402-11. doi: 10.1002/cncr.27795.

BACKGROUND:

Randomized clinical trials (RCT) have demonstrated equivalent survival for breast-conserving therapy with radiation (BCT) and mastectomy for early-stage breast cancer. A large, population-based series of women who underwent BCT or mastectomy was studied to observe whether outcomes

of RCT were achieved in the general population, and whether survival differed by surgery type when stratified by age and hormone receptor (HR) status.

METHODS:

Information was obtained regarding all women diagnosed in the state of California with stage I or II breast cancer between 1990 and 2004, who were treated with either BCT or mastectomy and followed for vital status through December 2009. Cox proportional hazards modeling was used to compare overall survival (OS) and disease-specific survival (DSS) between BCT and mastectomy groups. Analyses were stratified by age group (< 50 years and ≥ 50 years) and tumor HR status.

RESULTS:

A total of 112,154 women fulfilled eligibility criteria. Women undergoing BCT had improved OS and DSS compared with women with mastectomy (adjusted hazard ratio for OS entire cohort = 0.81, 95% confidence interval [CI] = 0.80-0.83). The DSS benefit with BCT compared with mastectomy was greater among women age ≥ 50 with HR-positive disease (hazard ratio = 0.86, 95% CI = 0.82-0.91) than among women age < 50 with HR-negative disease (hazard ratio = 0.88, 95% CI = 0.79-0.98); however, this trend was seen among all subgroups analyzed.

CONCLUSIONS:

Among patients with early stage breast cancer, BCT was associated with improved DSS. These data provide confidence that BCT remains an effective alternative to mastectomy for early stage disease regardless of age or HR status.

Hughes KS, Schaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-2387

Kunkler IH, Williams LW, Jack W, et al. The PRIME 2 trial: Wide local excision and adjuvant hormonal therapy \pm postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation. *SABCS 2013*, abstr. S2-1.

Smith BD, Buchholz TA. Radiation treatments after breast-conserving therapy for elderly patients. *J Clin Oncol* 2013;31:2367-8.

Tuschy B, Berlit S, Romero S, et al. Influence of age on short-term complications after intraoperative radiotherapy in women after breast-conserving surgery. *Anticancer Res* 2013;33:3995-9.

van de Water W, Bastiaannet E, Scholten AN, et al. Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2013 Nov 23. [Epub ahead of print]

RESULTS:

We included 5 randomized clinical trials comprising 3,190 patients. Overall, 39 % of the patients were ≥ 70 years old, and most had hormone receptor-positive T1 tumors without nodal involvement. All patients received adjuvant systemic therapy. Patients who received radiotherapy had a

lower relative risk of locoregional recurrence (pooled odds ratio [OR] 0.36; 95 % confidence interval [CI] 0.25-0.50). The 5-year absolute risk was 2.2 % (95 % CI 1.6-3.1) among patients who received radiotherapy, versus 6.5 % (95 % CI 5.3-7.9) among patients who did not. The absolute risk difference was 4.3 % (95 % CI 2.9-5.7), corresponding with a number needed to treat of 24. No differences were observed for distant recurrence or overall survival.

CONCLUSIONS:

Although patients who received radiotherapy had a lower relative risk of locoregional recurrence, the absolute risk was low, and overall survival was not affected. We propose that the debate should not only focus on the relative risk but also on the absolute benefit of radiotherapy and the number needed to treat. Both treatment options may be reasonable in clinical practice.

1a. Prognostic factors after BCS

New in 2013:

Hughes KS, Schaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382-2387

Smith BD, Buchholz TA. Radiation treatments after breast-conserving therapy for elderly patients. J Clin Oncol 2013;31:2367-8.

Vicini FA, Shaitelman S, Wilkinson JB, et al. Long-term impact of young age at diagnosis on treatment outcome and patterns of failure in patients with ductal carcinoma in situ treated with breast-conserving therapy. Breast J 2013;19:365-73. doi: 10.1111/tbj.12127.

Mamounas P. Predicting locoregional recurrence after neoadjuvant chemotherapy in breast cancer patients. Clin Adv Hematol Oncol 2013;11:175-177

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 2012;30:3960-6.

1b. Postmastectomy-RT (PMRT): Prognostic factors /application / receipt after postmastectomy RT

New in 2013:

Moo TA, McMillan R, Lee M, et al. Selection criteria for postmastectomy radiotherapy in t1-t2 tumors with 1 to 3 positive lymph nodes.

Ann Surg Oncol 2013;20:3169-74. doi: 10.1245/s10434-013-3117-0.

METHODS:

Between 1995 and 2006, a total of 1,331 patients with T1-T2 tumors and 1 to 3 positive ALN underwent mastectomy. We excluded T3/T4 tumors and neoadjuvant chemotherapy; we analyzed 1,087 patients (924 without PMRT, 163 with PMRT). Chi square testing compared clinicopathologic features between groups. The Kaplan-Meier method and Cox regression analysis examined the association between PMRT and LRR, RFS, and OS.

CONCLUSIONS:

By using clinicopathologic features, clinicians delivered PMRT to a select group of patients with T1-T2 tumors and 1 to 3 positive ALN, resulting in similarly low rates of 5-year LRR. Among patients not receiving PMRT, age ≤ 50 years and LVI were associated with increased LRR rates and warrant PMRT consideration.

Li Y, Moran MS, Huo Q, Yang Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. *PLoS One* 2013;8:e81765. doi: 10.1371/journal.pone.0081765.

CONCLUSIONS:

Our pooled analysis revealed that PMRT significantly reduces the risk of LRR in patients with T1-T2 tumors with 1-3 positive nodes, and the magnitude of the LRR risk reduction is slightly greater for larger tumors. Our results suggest that PMRT should be considered for patients with T1/T2 tumors with 1-3 positive nodes to decrease the relatively high risk of LRR.

Chen X, Yu X, Chen J, Yang Z, Shao Z, et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with t1-t2 disease and one to three positive lymph nodes after mastectomy. *Oncologist* 2013;18:141-147

Cheng SH, Tsai SY, Yu BL, et al. Validating a prognostic scoring system for postmastectomy locoregional recurrence in breast cancer. *Int J Radiat Oncol Biol Phys* 2013;85:953-8.

Hastings J, Iganej S, Huang C, et al. Risk Factors for Locoregional Recurrence After Mastectomy in Stage T1 N0 Breast Cancer. *Am J Clin Oncol* 2013 Feb 20. [Epub ahead of print]

Ma J, Li J, Xie J, Chen J, et al. Post mastectomy linac IMRT irradiation of chest wall and regional nodes: dosimetry data and acute toxicities. *Radiat Oncol* 2013;8:81.

MacDonald SM, Patel SA, Hickey S, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2013;86:484-90.

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys* 2014;88:65-72 epub: 2013 Oct 22. pii: S0360-3016(13)03108-8.

Truong PT, Sadek BT, Lesperance MF, et al. Is Biological Subtype Prognostic of Locoregional Recurrence Risk in Women With pT1-2N0 Breast Cancer Treated With Mastectomy? Int J Radiat Oncol Biol Phys 2014;88:57-64.

Wright JL, Takita C, Reis IM, et al. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. Cancer 2013;119:16-25.

Further references:

Dragun AE, Huang B, Gupta S, et al. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. Int J Radiat Oncol Biol Phys 2012;83:e591-6.

Duraker N, Demir D, Bati B, et al. Survival benefit of post-mastectomy radiotherapy in breast carcinoma patients with T1-2 tumor and 1-3 axillary lymph node(s) metastasis. Jpn J Clin Oncol 2012;42:601-608

Huang CJ, Hou MF, Chuang HY, et al. Comparison of clinical outcome of breast cancer patients with T1-2 tumor and one to three positive nodes with or without postmastectomy radiation therapy. Jpn J Clin Oncol 2012;42:711-20.

Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. J BUON 2012;17:245-8.

Tendulkar RD, Rehman S, Shukla ME, et al. Impact of postmastectomy radiation on locoregional recurrence in breast cancer patients with 1-3 positive lymph nodes treated with modern systemic therapy. Int J Radiat Oncol Biol Phys 2012;83:e577-81

2. Radiation therapy of regional lymphatics

New in 2013:

Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on clinical management of the axilla in older breast cancer patients: A SEER-Medicare analysis. Ann Surg Oncol 2013;20:4145-52

Chang JS, Park W, Kim YB, et al. Long-term survival outcomes following internal mammary node irradiation in stage II-III breast cancer: results of a large retrospective study with 12-year follow-up. Int J Radiat Oncol Biol Phys 2013;86:867-72.

Courdi A, Chamorey E, Ferrero J-M, et al. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. Radiother Oncol 2013;108:259-265.

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 2013;86:860-866.

Jagsi R, Pierce L. Radiation therapy to the internal mammary nodal region in breast cancer: the debate continues. Int J Radiat Oncol Biol Phys 2013;86:813-815

Karam I, Lesperance MF, Berrang T, et al. pN0(i+) Breast cancer: treatment patterns, locoregional recurrence, and survival outcomes. *Int J Radiat Oncol Biol Phys* 2013;87:731-737.

Kim SI, Cho SH, Lee JS, et al. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. *Br J Cancer* 2013;109:1165-71.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9.

Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.

Offersen BV, Nielsen HM, Overgaard M, Overgaard J. Is regional nodes radiotherapy an alternative to surgery? *Breast* 2013;22 Suppl 2:S118-28. doi: 10.1016/j.breast.2013.07.023.

Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013;49 (Suppl 3): S1 abstract BA2

Rutgers EJ, Donker M, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial (10981/22023. J Clin Oncol 2013;31,Abstract LBA1001.

Systematic review protocol for treatment of the axilla: Goyal A, Duley L, Fakis A. Axillary treatment for patients with early breast cancer and lymph node metastasis: systematic review protocol. World J Surg Oncol 2013;11:6

3. Radiation therapy – late normal tissue complications and long-term cosmesis; IMRT vs. standard RT using wedged tangential fields; Boost RT

New in 2013:

Meta-analysis:

Tzikas A, Komisopoulos G, Ferreira BC, et al. Radiobiological evaluation of breast cancer radiotherapy accounting for the effects of patient positioning and breathing in dose delivery. A meta analysis. Technol Cancer Res Treat 2013;12:31-44. doi: 10.7785/tcrt.2012.500274.

Further references in 2013:

Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. J Clin Oncol 2013;31:4488-4495.

There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

CONCLUSION:

Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

See also comment on this issue: Kavanagh BD, Rabinovitch R, Mohideen N. Improved cosmesis in early breast cancer using conformal radiotherapy. J Clin Oncol 2013;31:4483-4485

Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. Radiother Oncol 2013;108:293-8. doi: 10.1016/j.radonc.2013.07.006.

The dose-volume effect of radiation therapy on breast tissue is poorly understood. We estimate NTCP parameters for breast fibrosis after external beam radiotherapy.

MATERIALS AND METHODS:

We pooled individual patient data of 5856 patients from 2 trials including whole breast irradiation followed with or without a boost. A two-compartment dose volume histogram model was used with boost volume as the first compartment and the remaining breast volume as second compartment. Results from START-pilot trial (n=1410) were used to test the predicted models.

CONCLUSIONS:

This large multi-centre pooled study suggests that the effect of volume parameter is small and the maximum RT dose is the most important parameter to influence breast fibrosis. A small value of volume parameter 'n' does not fit with the hypothesis that breast tissue is a parallel organ. However, this may reflect limitations in our current scoring system of fibrosis.

Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomised trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. *J Clin Oncol* 2013;31:4038-45

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Is the simultaneously integrated boost (SIB) technique for early breast cancer ready to be adopted for routine adjuvant radiotherapy ? Statement of the German and the Austrian Societies of Radiooncology (DEGRO / ÖGRO). *Strahlenther Onkol* 2013;189:193-196

Zhou Y, Zhou W, Liu Q, et al. XRCC1 R399Q polymorphism and risk of normal tissue injury after radiotherapy in breast cancer patients. *Tumour Biol* 2013 Dec 3. [Epub ahead of print]

The meta-analysis suggests that XRCC1 R399Q polymorphism was significantly associated with increased risk of normal tissue injury after radiotherapy in breast cancer patients, and XRCC1 R399Q polymorphism is a genetic marker of normal tissue injury after radiotherapy in breast cancer patients.

4. Cardiac toxicity in breast cancer patients treated with radiation therapy (PMRT or following BCS)

New in 2013:

Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-98. doi: 10.1056/NEJMoA1209825. In response: Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med* 2013;368:2527. doi: 10.1056/NEJMc1304601.

Mast ME, van Kempen-Harteveld L, Heijenbrok MW, et al. Left-sided breast cancer radiotherapy with and without breath-holding: does IMRT reduce the cardiac dose even further? *Radiother Oncol* 2013;108:248-53

Taylor C, Darby SC. Ischemic heart disease and breast cancer radiotherapy: The way forward. *JAMA Intern Med* 2014;174:160-1

Tjessem KH, Johansen S, Malinen E, et al. Long-term cardiac mortality after hypofractionated radiation therapy in breast cancer. *Int J Radiat Oncol Biol Phys* 2013;87:337-343.

Vaidya JS, Bulsara M, Wenz F. Ischemic heart disease after breast cancer radiotherapy. *N Engl J Med* 2013;368:2526-7

5. Sequencing RT and chemotherapy

Fowble B. Local-regional management issues for the radiation oncologist in the neoadjuvant chemotherapy setting. SABCS 2013, abstr.

Hickey BE, Francis DP, Lehman M. Sequencing of chemotherapy and radiotherapy for early breast cancer. *Cochrane Database Syst Rev* 2013 Apr 30;4:CD005212. doi: 10.1002/14651858.CD005212.pub3

National Comprehensive Cancer Network (NCCN-USA). Clinical Practice Guidelines in Oncology: Breast Cancer - Version V.3.2013:

Radiation therapy should follow chemotherapy when chemotherapy indicated

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys* 2014;88:65-72.

Wright JL, Takita C, Reis IM, et al. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer* 2013;119:16-2

2012:

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol* 2012;30:3960-6.

6. Radiation therapy after breast-conserving surgery

6.1 New LoE for special topics which might impact daily clinical practice: Hypofractionating, APBI including IORT

New in 2013:

Classification system for identifying women at risk for altered partial breast irradiation recommendations after breast magnetic resonance imaging

Kowalchik KV, Vallow LA, McDonough M, et al. Classification system for identifying women at risk for altered partial breast irradiation recommendations after breast magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2013;87:127-33.

Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomised trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. *J Clin Oncol* 2013;31:4038-45

Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202

Smith BD, Buchholz TA. Radiation treatments after breast-conserving therapy for elderly patients. *J Clin Oncol* 2013;31:2367-8.

6.2. Hypofractionating

Hypofractionated radiotherapy: Should hypofractionating be the new standard for radiation therapy following BCS?

New in 2013:

Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol* 2013;14:1086-1094

See also comment: Haffty BG, Buchholz TA: Hypofractionated breast radiation: preferred standard of care? *Lancet Oncol* 2013;14:1032-33

6.3. Short course RT with simultaneous integrated boost (SIB)-RT

New in 2013:

Freedman GM, White JR, Arthur DW, et al. Accelerated fractionation with a concurrent boost for early breast cancer. *Radiother Oncol* 2013;106:15-20

6.4. Indications, limitations and cautions regarding APBI including IORT

New in 2013:

Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomised trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. *J Clin Oncol* 2013;31:4038-45

Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202

Tuschy B, Berlit S, Romero S, et al. Influence of age on short-term complications after intraoperative radiotherapy in women after breast-conserving surgery. *Anticancer Res* 2013;33:3995-9.

Tuschy B, Berlit S, Romero S, et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. *Radiat Oncol* 2013;8:95. doi: 10.1186/1748-717X-8-95.

Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013;14:1269-77. doi: 10.1016/S1470-2045(13)70497-2.

6.5. Technical aspects / new techniques regarding delivery of RT, in particular delivery APBI / IMRT, and toxicity regarding simultaneous integrated boost radiotherapy (SIB)

New in 2013:

Appelt AL, Vogelius IR, Bentzen SM. Modern hypofraction schedules for tangential whole breast irradiation decrease the fraction size-corrected dose to the heart. *Clin Oncol (R Coll Radiol)* 2013;25:147-25. doi: 10.1016/j.clon.2012.07.012

Bantema-Joppe EJ, Vredevelde EJ, de Bock G, et al. Five years outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. *Radiother Oncol* 2013;108:269-272

Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013;31:4488-4495.

There are few randomized controlled trial data to confirm that improved homogeneity with simple intensity-modulated radiotherapy (IMRT) decreases late breast tissue toxicity. The Cambridge Breast IMRT trial investigated this hypothesis, and the 5-year results are reported.

CONCLUSION:

Improved dose homogeneity with simple IMRT translates into superior overall cosmesis and reduces the risk of skin telangiectasia. These results are practice changing and should encourage centers still using two-dimensional RT to implement simple breast IMRT.

See also comment on this issue: Kavanagh BD, Rabinovitch R, Mohideen N. Improved cosmesis in early breast cancer using conformal radiotherapy. *J Clin Oncol* 2013;31:4483-4485

Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;108:293-8. doi: 10.1016/j.radonc.2013.07.006.

Further references:

Lorenzen EL, Taylor CW, Maraldo M, et al. Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: a multi-centre study from Denmark and the UK. *Radiother Oncol* 2013;108:254-8. doi: 10.1016/j.radonc.2013.06.025.

Quinn A, Holloway L, Hardcastle N, et al. Normal tissue dose and second cancer risk due to megavolt fan-beam CT, static tomotherapy and helical tomotherapy in breast radiotherapy. *Radiother Oncol* 2013;108:266-268

Stieler F, Wenz F, Shi M, Lohr F. A novel surface imaging system for patient positioning and surveillance during radiotherapy. A phantom study and clinical evaluation. *Strahlenther Onkol* 2013;189:938-44. doi: 10.1007/s00066-013-0441-z

Tzikas A, Komisopoulos G, Ferreira BC, et al. Radiobiological evaluation of breast cancer radiotherapy accounting for the effects of patient positioning and breathing in dose delivery. A meta analysis. *Technol Cancer Res Treat* 2013;12:31-44. doi: 10.7785/tcrt.2012.500274.

7. Long-term cosmesis WBI +/- boost

New in 2013:

Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;108:293-8. doi: 10.1016/j.radonc.2013.07.006.

8. APBI by use of IORT / interstitial brachytherapy / external beam irradiation administered as sole radiation therapy modality immediately after breast conserving surgery

New in 2013:

Aristei C, Palumbo I, Capezzali G, et al. Outcome of a phase II prospective study on partial breast irradiation with interstitial multi-catheter high-dose rate brachytherapy. *Radiother Oncol* 2013;108:236-241

Krengli M, Calvo FA, Sedlmayer F, et al. Clinical and technical characteristics of intraoperative radiotherapy: Analysis of the ISIIORT-Europe database. *Strahlenther Onkol* 2013;189:729-737.

Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. Accelerated partial breast irradiation with intraoperative electrons: Using GEC-ESTRO recommendations as guidance for patient selection. *Radiother Oncol* 2013;106:21-7

Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomised trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. *J Clin Oncol* 2013;31:4038-45

Polgar C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202

Stewart AJ, Hepel JT, O'Farrell DA, et al. Equivalent uniform dose for accelerated partial breast radiation using the MammoSite applicator. *Radiother Oncol* 2013;108:232-235

Tuschy B, Berlitz S, Nasterlack C, et al. Intraoperative radiotherapy of early breast cancer using low-kilovoltage x-rays - reasons for omission of planned intraoperative irradiation. *Breast J* 2013;19:325-8

Vaidya JS, Wenz F, Bulsara M, et al.; on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2013 Nov 8. doi:pii: S0140-6736(13)61950-9. 10.1016/S0140-6736(13)61950-9.

Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269-77. doi: 10.1016/S1470-2045(13)70497-2.

9. Boost-RT to the tumor (region) prior versus after BCS:

New in 2013:

Fastner G, Sedlmayer F, Merz F, et al. on behalf of the ISIORT Europe. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT Pooled Analysis. Radiother Oncol 2013; 108:279-86

Sedlmayer F, Sautter-Bihl ML, Budach W, Dunst J, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Is the simultaneously integrated boost (SIB) technique for early breast cancer ready to be adopted for routine adjuvant radiotherapy? Statement of the German and the Austrian Societies of Radiooncology (DEGRO / ÖGRO). Strahlenther Onkol 2013; 189:193-196

Van der Leij F, Elkhuisen PH, Janssen TM. External beam partial breast irradiation: difference in pre- and postoperative target volume delineation. Radiother Oncol 2012;103:S250. - *In consequence: PAPBI-Trial = Preoperative Accelerated Partial Breast Irradiation (PAPBI) using cone-beam technique in preop APBI-Boost-RT! (NCT01024582-Phase II-trial). Surgery 6 weeks after PAPBI.*

10. Randomized clinical trials in breast cancer regarding radiooncological issues

Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol 2013;14:1086-1094

NORA-Survey: "International survey of nodal radiotherapy in the era of personalized surgery of the axilla for early breast cancer" (Belkacemi et al.)

NSABP B-35. A clinical trial comparing anastrozole with tamoxifen in postmenopausal patients with DCIS undergoing lumpectomy with radiation therapy: <http://www.clinicaltrials.gov/ct2/show/NCT00053898>. Accessed February 4, 2011

NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation vs. partial breast irradiation for women with stage 0, I, or II breast cancer: <http://www.clinicaltrials.gov/ct/show/NCT00103181>. Accessed February 4, 2011.

NSABP B-43. A phase III trial comparing trastuzumab given concurrently with radiation therapy and radiation therapy alone for women with HER-2 positive DCIS resected by lumpectomy: <http://www.clinicaltrials.gov/ct2/show/NCT00769379>. Accessed February 4, 2011.

PAPBI-Trial = Preoperative Accelerated Partial Breast Irradiation (PAPBI) using cone-beam technique in preop APBI-Boost-RT! (NCT01024582-Phase II-trial). Van der Leij F, Elkhuisen PH, Janssen TM. External beam partial breast irradiation: difference in pre- and postoperative target volume delineation. *Radiother Oncol* 2012;103:S250

Venables K, Tsang Y, Ciurlionis L, Coles CE, Yarnold JR. Does participation in clinical trials influence the implementation of new techniques? A look at changing techniques in breast radiotherapy in the UK. *Clin Oncol (R Coll Radiol)* 2012;24:e100-5.

Williams LJ, Kunkler IH, King CC. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. *Health Technol Assess* 2011;i-xi, 1-57

10.1. Randomized clinical trials in breast cancer regarding APBI:

Armaroli L, Barbieri E, Bertoni F, et al. Breast cancer with low risk of local recurrence: partial and accelerated radiation with three-dimensional conformal radiotherapy (3DCRT) vs. standard radiotherapy after conserving surgery (phase III study). Version 01.05. 2007. Available from: http://groups.eortc.be/radio/res/irma/synopsis_trial_irma1.pdf

Phase III randomized clinical trials with 3D-EBCRT (external beam conformal radiotherapy) as experimental arm:

NSABP B-39/RTOG 0413: A randomized phase III study of conventional whole breast irradiation vs. partial breast irradiation for women with stage 0, I, or II breast cancer: <http://www.clinicaltrials.gov/ct/show/NCT00103181>. (opened accrual in 2005)

RAPID (randomized trial of accelerated partial breast irradiation)/Ontario clinical oncology group. Launched 2006: Olivotto IA, Whelan TJ, Parpia S, et al. *J Clin Oncol* 2013;31:4038-45

IRMA (Innovazioni nella Radioterapia della MAMmella). Launched 2006

GEC-ESTRO-trial

IMPORT-LOW (Intensity Modulated and Partial Organ RadioTherapy)-trial launched in 2006 as an extension to the START trials.

ELIOT (electron intraoperative therapy)-trial: Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013;14:1269-77

TARGIT trial (targeted intra-operative radiotherapy) trial: Vaidya JS, Wenz F, Bulsara M, et al.; on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2013 Nov 8. doi:pii: S0140-6736(13)61950-9. 10.1016/S0140-6736(13)61950-9.

10.2. Ongoing RCT, recruitment ended, further, interims or (more) mature results awaited in 2014

MRC/EORTC (BIG 2-04) SUPREMO Trial: Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial.

Kunkler IH, Canney P, van Tienhoven G, Russell NS; MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group.

SHARE. A French multicenter phase III trial comparing accelerated partial irradiation (APBI) versus standard or hypofractionated whole breast irradiation in low risk of local recurrence breast cancer. Belkacemi Y, Bourgier C, Kramar A, et al. SABCS 2012; OT1-2-02

TARGIT-A trial: Vaidya JS, Wenz F, Bulsara M, et al.; on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2013 Nov 8. doi:pii: S0140-6736(13)61950-9. 10.1016/S0140-6736(13)61950-9.

UK START (Standardisation of Breast Radiotherapy) Trials: Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol 2013;14:1086-1094

10.3. Ongoing Phase III RCT of hypofractionated WBI comparing sequential tumor bed boost to concurrent boost (still accruing pts.)

Freedman et al. Radiother Oncol 2013;106:15-20

RTOG 1005

IMPORT HIGH (Intensity Modulation and Partial Organ Radiation Therapy)

IMRT MC2

10.4. Radiotherapy in patients with pathologic response (e.g. ypT0 ypN0) after preoperative chemotherapy and mastectomy or BCS:

NCT01279304: Maastricht Radiation Oncology – register trial: Radiotherapy After Primary Chemotherapy for Breast Cancer (RAPCHEM) trial (NCT01279304).

10.5. Preoperative radiotherapy in patients with progression during or incomplete neoadjuvant chemotherapy:

NCT01618357: Sidney Kimmel Comprehensive Cancer Center: Pre-Operative Radiation With Incomplete Neo-Adjuvant Chemotherapy for Breast Cancer

10.6. DCIS: trials

NSABP B-43: A phase III clinical trial to compare trastuzumab (T) given concurrently with radiation therapy (RT) to RT alone for women with HER2+ DCIS resected by lumpectomy (Lx). Cobleigh MA, Anderson SJ, Julian TB, et al. SABCS 2012; OT1-2-01

RTOG 9804 –DCIS:

McCormick B. RTOG 9804: A prospective randomized trial for “good risk” ductal carcinoma in situ (DCIS), comparing radiation (RT) to observation (OBS). J Clin Oncol 2012;30 (suppl; abstr 1004).

McCormick B, Moughan J, Hudis C, Kuerer H et al. Low-risk breast ductal carcinoma in situ (DCIS): results from the Radiation Therapy Oncology Group 9804 Phase 3 Trial. Int J Radiat Oncol Biol Phys 2012;84(5) Suppl., S5, abstract 11: *In this “good risk” subset of DCIS, the LF rate was decreased significantly with the addition of RT. Longer follow-up is planned, as late failures continue to occur.*

11. Adjuvant Radiotherapy – actual topics and areas of uncertainty

Questions – areas of controversies - ongoing clinical trials - what we (still) need to know

- Subgroups suitable for to claim any RT for DCIS or invasive carcinoma?
 - DCIS/invasive cancer: no subgroup even with pure DCIS and low-risk criteria that does not benefit from RT in terms of decreased local recurrence: ongoing trials, confirming data in 2013; no significant long-term toxicity from RT; Boost-RT: benefit of additional boost radiotherapy for invasive breast cancer has been demonstrated in RCT with most benefit in younger patients. The role of boost radiotherapy in patients with pure DCIS is now being investigated in ongoing RCT and might be substantial for young patients.
 - Pure DCIS: newest data from RCT confirm the benefit of adding radiotherapy to breast conserving surgery for the treatment of all women diagnosed with DCIS. No long-term toxicity from use of radiotherapy was identified. However, the impact of RT is limited to local control by decreasing recurrence rate. Up to 15 year of follow-up, RCT which evaluated the role of additional RT failed to demonstrate overall survival benefit. Ongoing trials; role of molecular/genetic biomarkers has to be defined
 - DCIS: impact of RT by the fact that recent data not showing survival benefit?: ongoing trials; role of molecular/genetic biomarkers
- Subgroups suitable for (accelerated) partial breast irradiation / IORT after BCS?
 - Comparative effectiveness of WBI vs. PBI or APBI? For which subgroup equal effectiveness is considered?: ongoing trials
 - Used as definitive radiotherapy without external WBI? Limited to interstitial PBI (GEC-ESTRO)? Still an open question
- Fraction size: hypofractionation (hf) vs standard fractionation (nf) regimens?

- Comparative effectiveness of fractionation regimens? Hf equivalent and also accepted to be a “new” standard ? For which subgroup?: still a matter of debate and controversies regarding selection criteria identifying patients as well as subgroups of patients, for whom it might be more or equally effective and safe compared with normofractionated schedules. Ongoing trials!

RT fraction size, esp. (accelerated) hypofractionation: UK START-Trials demonstrated no inferiority to WBI after 10-year follow-up (10 yrs f/u 2013).

However, some scientific boards consider hyperfractionated RT to be equivalent to normofractionated RT recommending hf-RT as optional alternative in some guidelines. Even more, hypofractionation is considered to be “the new standard” in some countries. If hypofractionated RT is the chosen schedule, single fraction dose of 2.66 Gy up to a total dose of 39-42 Gy in 15 or 16 fractions is recommended in international guidelines. See also critical remarks regarding hypofractionation in the updated DEGRO Practice Guidelines 2013 (references see: *I.* in front of this slice!)

- Hypofractionation even, when boost RT is indicated? Majority of patients in RCTs (e.g. START-trials) received sequential boost-RT after hf-RT!
- Post-mastectomy irradiation (PMRT) of the thoracic wall:
 - Risk factors? Who are at risk for developing relapse, particularly the “intermediate risk” subgroup (RR: 10-20%; T1-2 and N+(1-3), G3, vascular invasion, lobular subtype; >T2 N0; pT3, N0; N+(1-3), etc) ? New data from RCTs confirm benefits from RT for “intermediate risk” pts.
 - survival benefit even for pT1-2 pN+(0-3) after mastectomy (LoE 2b); documented for patients after BCS (LoE 1a):

Postmastectomy radiotherapy (PMRT) in „intermediate risk“-patients - further informations:

Effects of adjuvant RT on cardiovascular mortality differ according to primary tumor location in node-negative patients

Effects of adjuvant radiotherapy on mortality differ according to primary tumor location in node-positive patients:

Lymphonodal micrometastasis or isolated tumor cells are associated with poorer survival compared to pN0 disease: new data show: LRR appears similar for women with pN0(i+) compared to their pN0-counterparts (but keep in mind: limitation of small available sample size of pN0(i+-patients).

pN0(i+) vs pN0 pts. outcome: Outcome (OS, LRR) of pN0(i+) pts. appears similar to matched pN0 counterparts.

- In patients with positive SNB but no axilla dissection? New data from RCTs: pN0-patients with central/medial tumor benefit from PMRT
- Positive margins but no further surgery? No new data from RCTs

- After pathological (complete?) response to preoperative chemotherapy (NACT)? ongoing prospective register study: RAPCHEM

RT after neoadjuvant chemotherapy (NACT) in pts reaching ypT0, pN0: retrospective data from KROG 12-05 trial (Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 2014;88:65-72)

- Boost RT to the tumor bed following BCS?
 - No subgroup that does not benefit from boost RT in terms of decreased local recurrence. Boost-RT for young pats with DCIS?: ongoing trials; up to now, no mature data of RCTs yet available
 - Simultaneously integrated boost RT (SIB): ongoing RCT; no mature data from RCTs; see statement of the DEGRO/ÖGRO Expert Panel 2013
 - Should SIB replace sequential PBI boost in the context of WBI?: ongoing RCTs; no mature data from RCTs
- Which locoregional lymphatics have to be irradiated?
 - Post surgery: which nodal areas? Axilla, periclavicular, mammaria interna lymphatics? New data from RCTs and one new meta-analysis show some benefits for distinguished subgroups of patients
 - Post PST, even, if primary tumor is responsive to primary systemic treatment: no mature data from RCT; ongoing trials: NCT01279304: RAPCHEM
- Impact of advanced technologies?
 - External beam conformal RT techniques: 3D-CRT, IMRT, Tomotherapy, VMAT, Protons, IGRT, SIB
 - contouring guidelines for RT: RTOG Breast Cancer Atlas; national guidelines+contouring atlas by the Danish Breast Cancer Cooperative Group 2013

Contouring guidelines for RT: RTOG Breast Cancer Atlas; national guidelines+contouring atlas by the Danish Breast Cancer Cooperative Group:

Nielsen MH, Berg M, Pedersen AN, et al; Danish Breast Cancer Cooperative Group Radiotherapy Committee. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol 2013;52:703-10

- *New techniques used for APBI approaches:*

External beam conformal radiation therapy techniques:

a) 3 dimensional conformal radiation therapy (3D-CRT)

The most widely used 3D-CRT approach uses multiple (three to five) tangentially static positioned non-coplanar beams with static photons, and/or electrons fields. The tumor bed is defined by the computed tomography visualized seroma cavity, postoperative changes, and surgical clips, when available. The clinical target volume (CTV) is defined as the tumor bed with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall. The planning tumor volume (PTV) is defined as the CTV with a 1.0 cm uniform three-dimensional expansions. This expansion accounts for potential breathing and setup errors and hence this approach might deliver higher doses to normal breast tissue than IMRT–APBI. This technique was adopted for use as one of the allowed treatment modalities for patients randomized to APBI in the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology group (NSABP/RTOG) 0413 phase III trial. The prescription dose used for NSABP/RTOG protocol is 3.85 Gy twice daily (separated by at least 6 h) to a total dose of 38.5 Gy delivered within 1 week [Njeh et al. 2012].

b) Intensity modulated radiation therapy (IMRT):

Intensity modulated radiation therapy (IMRT) is a form of external beam radiation therapy (EBRT) that uses complex structure-based planning techniques and variable intensity beam fluencies to optimize dose delivery.

The major value of IMRT for breast radiotherapy is reduction of dose inhomogeneity within the target volume. A secondary advantage is the reduction of high dose irradiation to some normal tissues and organ at risk (OAR) such as the heart and ipsilateral lung. These have been supported by several studies comparing IMRT with standard 3D tangential field radiation therapy for breast cancer. However, the multiple beams in IMRT could results in a substantial volume of normal tissue receiving a low or moderate radiation dose (i.e. increase in integral dose) [Njeh et al. 2012].

c) Tomotherapy:

Helical tomotherapy (“slice therapy”) combines helical intensity modulated (IM) delivery with an integrated image guided (IG) system using machine specifically designed for IMRT delivery. In tomotherapy the patient moves through the bore of the gantry simultaneously with gantry rotation. Radiation is delivered by a narrow 6 MV beam rotating around the patient analogous to computed tomography. Online imaging is achieved by using megavoltage computed tomography (MVCT) scans acquired with the linear accelerator. Because of the integration of IMRT and image guided radiation therapy (IGRT), tomotherapy has potential for breast treatment and especially APBI [Njeh et al. 2012].

d) Volumetric modulated arc therapy (VMAT) or intensity-modulated arc therapy (IMAT):

Volumetric modulated arc therapy (VMAT) also known as, intensity-modulated arc therapy (IMAT), delivers highly conformal dose distributions by combining gantry rotation and dynamic multileaf collimation. Instead of delivering intensity-modulated beams with fixed gantry angles, VMAT delivers optimized dose distributions by rotating the radiation beam around the patient. During delivery, the field shape, which is formed by a multileaf collimator (MLC), changes continuously as determined by the treatment plan. Intensity distributions at all angles around the patient are achieved with multiple overlapping arcs, with each arc having a different set of field apertures. The weight or the total monitor units (MUs) delivered in each arc, are typically different. VMAT uses intensity-modulated fan beams rotating around the patient, delivering the treatment slice

by slice. As with tomotherapy, VMAT combines intensity modulation and rotational delivery. Recently several VMAT delivery techniques have been developed for clinical applications, including RapidArc (Varian, CA) and VMAT (Elekta AB, Stockholm, Sweden).

Compared to a conventional 3D-CRT technique VMAT is considered to be more efficient, rendering equivalent or better dose conformity, delivers lower doses to the ipsilateral lung and breast [Njeh et al. 2012].

Mandatory: Improvement of risk stratification of patients in order to select individualized optimal radiooncological treatment for each individual

12. Prognostic outcome of local/regional recurrence in breast cancer pts. treated by BCS + RT as their first site of failure:

Shenouda M, Sadek BT, Abi Raad RF, Goldberg SI, et al. Prognostic outcomes of local-regional recurrence in breast cancer patients treated by breast-conservation treatment. Int J Radiat Oncol Biol Phys 2012;84(5) Suppl., S36, abstract 89: *With a long follow-up, patients who develop LRR as first event have a 56% 10-year overall survival. The interval between diagnosis and breast failure, multiple LRR, type of recurrence and surgical treatment were significantly prognostic factors for the overall survival.*

Hannoun-Levi JM, Resch A, Gal J, et al. ; GEC-ESTRO Breast Cancer Working Group. Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. Radiother Oncol 2013;108:226-231

13. Excess mortality for long-term survivors of breast cancer:

New in 2013/2014:

Janssen-Heijnen ML, van Steenbergen LN, Voogd AC, et al. Small but significant excess mortality compared with the general population for long-term survivors of breast cancer in the Netherlands. Ann Oncol 2014;25:64-8. doi: 10.1093/annonc/mdt424.

BACKGROUND:

Coinciding with the relatively good and improving prognosis for patients with stage I-III breast cancer, late recurrences, new primary tumours and late side-effects of treatment may occur. We gained insight into prognosis for long-term breast cancer survivors.

PATIENTS AND METHODS:

Data on all 205 827 females aged 15-89 diagnosed with stage I-III breast cancer during 1989-2008 were derived from the Netherlands Cancer Registry. Conditional 5-year relative survival was calculated for every subsequent year from diagnosis up to 15 years.

RESULTS:

For stage I, conditional 5-year relative survival remained ~95% up to 15 years after diagnosis (a stable 5-year excess mortality rate of 5%). For stage II, excess mortality remained 10% for those aged 15-44 or 45-59 and 15% for those aged 60-74. For stage III, excess mortality decreased from 35% at diagnosis to 10% at 15 years for those aged 15-44 or 45-59, and from ~40% to 30% for those aged ≥ 60 .

CONCLUSIONS:

Patients with stage I or II breast cancer had a (very) good long-term prognosis, albeit exhibiting a small but significant excess mortality at least up to 15 years after diagnosis. Improvements albeit from a lower level were mainly seen for patients who had been diagnosed with stage III disease. Caregivers can use this information to better inform (especially disease-free) cancer survivors about their actual prognosis.

14. Secondary neoplasia following adjuvant radiotherapy for breast cancer:

New in 2013:

Grantzau T, Mellemkjaer L, Overgaard J. Second primary cancers after adjuvant radiotherapy in early breast cancer patients: a national population based study under the Danish Breast Cancer Cooperative Group (DBCCG). *Radiother Oncol* 2013;106:42-49

Quinn A, Holloway L, Hardcastle N, et al. Normal tissue dose and second cancer risk due to megavoltage fan-beam CT, static tomotherapy and helical tomotherapy in breast radiotherapy. *Radiother Oncol* 2013;108:266-8.

Allgemeine Aspekte adjuvanter RT:

Zhou J, Griffith KA, Hawley ST, et al. Surgeons' knowledge and practices regarding the role of radiation therapy in breast cancer management. *Int J Radiat Oncol Biol Phys* 2013;87:1022-9.

PURPOSE:

Population-based studies suggest underuse of radiation therapy, especially after mastectomy. Because radiation oncology is a referral-based specialty, knowledge and attitudes of upstream providers, specifically surgeons, may influence patients' decisions regarding radiation, including whether it is even considered. Therefore, we sought to evaluate surgeons' knowledge of pertinent risk information, their patterns of referral, and the correlates of surgeon knowledge and referral in specific breast cancer scenarios.

METHODS AND MATERIALS:

We surveyed a national sample of 750 surgeons, with a 67% response rate. We analyzed responses from those who had seen at least 1 breast cancer patient in the past year (n=403), using logistic regression models to identify correlates of knowledge and appropriate referral.

RESULTS:

Overall, 87% of respondents were general surgeons, and 64% saw >10 breast cancer patients in the previous year. In a scenario involving a 45-year-old undergoing lumpectomy, only 45% correctly estimated the risk of locoregional recurrence without radiation therapy, but 97% would refer to radiation oncology. In a patient with 2 of 20 nodes involved after mastectomy, 30% would neither refer to radiation oncology nor provide accurate information to make radiation decisions. In a patient with 4 of 20 nodes involved after mastectomy, 9% would not refer to radiation oncology. Fewer than half knew that the Oxford meta-analysis revealed a survival benefit from radiation therapy after lumpectomy (45%) or mastectomy (32%). Only 16% passed a 7-item knowledge test; female and more-experienced surgeons were more likely to pass. Factors significantly associated with appropriate referral to radiation oncology included breast cancer volume, tumor board participation, and knowledge.

CONCLUSIONS:

Many surgeons have inadequate knowledge regarding the role of radiation in breast cancer management, especially after mastectomy. Targeted educational interventions may improve the quality of care.

Do radiation therapy is needed even in small invasive breast cancers and DCIS following BCS ?

White J. Do we need to irradiate all small invasive breast cancers and DCIS? Am Soc Clin Oncol Educ Book 2013;40-4. doi: E10.1200/EdBook_AM.2013.33.40.

Who should not undergo breast conservation? *In all patients where radiotherapy cannot be given.*

Nijenhuis MV, Rutgers EJ. Who should not undergo breast conservation? Breast 2013;22 Suppl 2:S110-4. doi: 10.1016/j.breast.2013.07.021.

Abstract

Optimal local control is one of the three main aims of breast cancer treatment (next to optimal regional control and reducing the risk of distant relapses by adequate systemic treatments). To this end, many women desire breast conservation provided local control is comparable to that of ablative procedures, the cosmetic outcome is good and side effects of treatment are limited. To achieve this delicate balance the following should be part of the information to the patient with an operable breast cancer: Patients should have an open discussion with their care providers to enable a shared decision: this will lead to less anxiety and stress with the best satisfaction and recovery. The possibility of breast conservation should always be explored. Even with equal local control and survival outlook, quite a minority (about 20%) of patients opt for ablative procedures (with or without breast reconstruction). Higher risk of local relapse (i.e. persistent cancer growth in the breast) is associated with higher risk of distant disease and subsequent risk of dying of breast cancer. Rough estimates indicate that for every four local relapses one patient may die from breast cancer due to persistent disease. This estimate may vary substantially with the type of cancers (see dr. Morrow), age at diagnosis, application and duration of systemic treatments. To limit the negative effect on overall survival through local relapses, it is generally accepted that for early breast cancer local relapse rates should be within the limit of 1% per year, or within 10% at 10 years. Current population based overviews and hospital based studies show that the risk of local relapse after breast conservations are very well below this limit, being around 2-3% at 5 years. There is no absolute risk threshold of local relapse incidence above which breast conservation is absolutely contra indicated: this will remain an individual

decision. Oncoplastic procedures should widely be available to adjust to the width of the local excision and to improve cosmetic outcome. In larger cancers, the option of neo-adjuvant chemotherapy must be considered: about one-third of "mastectomy candidates" can be converted to an oncologically safe breast conservation. The most important independent risk factors for a breast relapse are: more than focally incomplete margins (roughly 2 times increased risk), young age (<35 years, 2 times increased risk) no radiotherapy (2-4 times increased risk). These risk factors again may also be influenced by the biological type of breast cancer. Combination of risk factors should be added: e.g. young women (<35 years) who had breast conservation for DCIS without radiotherapy may face 15 years breast relapse rate of over 40%. In aggregate, in the following clinical situations the increased risk of breast relapse should be extensively discussed with the patient and breast conservation should be executed with caution: Very young women (<35 years) Extensive DCIS (heralded by extensive microcalcifications) mounting up to one quarter of the breast, particularly in women under 40 years of age. More than focally incomplete resection of an invasive or in situ cancer. Radiotherapy cannot be given. The following factors should, as it stands, not be considered as a contra indication for breast conservation: multi-focal breast cancer, multi-centric breast cancer, the location of the cancer in the breast (including retro areola location), vascular invasion and lobular histology. All with the provision that by the breast conserving surgery complete margins a good cosmetic outcome should be achieved.

For further informations on radiooncological issues:

See also: Goyal S, Buchholz T, Haffty B. Breast Cancer: Early Stage. In: Perez and Brady's Radiation Oncology, 6th edn. 2013.

Treatment of breast cancer ideally requires a multidisciplinary approach. For most patients with invasive breast cancer, the recommended treatment is surgical resection of the primary tumor with assessment of axillary lymph nodes; adjuvant systemic treatment with chemotherapy, endocrine and/or targeted therapy, or combination of all, and adjuvant radiation therapy.

The equivalence of breast conserving therapy (BCT) to mastectomy in the treatment of women with early-stage breast cancer has been demonstrated in several phase III trials with over 25 years of follow-up. Despite the undisputed efficacy of this treatment approach, recent investigations have explored methods to either reduce the overall time, inconvenience or toxicity of its application. These approaches have included (1) accelerating the dose delivery scheme, (2) reducing the treatment target to less than whole breast, or (3) identifying subgroups of women in which adjuvant radiation therapy (RT) following lumpectomy can be safely omitted

Accelerated partial breast irradiation (APBI) has been investigated as a possible option that incorporates both a decrease in the overall treatment time and a reduction in the amount of normal tissue irradiated.

Radiation kills cells largely through the generation of free radicals, which deposit large amounts of energy that cause single- and double-strand breaks in the cell's DNA. The aim and clinical goal of radiation treatment is to eradicate tumor cells selectively, without injuring normal tissue in irradiated fields. In general, tumors are less able to repair DNA damage than are normal tissues and more frequently are in radiosensitive cell-cycle phases, such as mitosis.

Division of the radiation dose into a number of treatment fractions, i.e. fractionated radiation therapy, provides two important biologic advantages: it allows DNA repair to take place within the normal tissues and allows proliferating tumor cells to redistribute through the cell cycle and move into the more radiosensitive phase.

Indications for postmastectomy radiotherapy (PMRT) and regional radiotherapy are independent from the amount of surgery and the administration of adjuvant systemic treatments (LoE 1a).

Radiation therapy continues to provide a significant benefit, both statistically and clinically: Radiation therapy has been shown to minimize the risk of local recurrence after mastectomy and lumpectomy in a breast conserving treatment concept (in-field recurrences) by 70% (LoE 1a), respectively. Regarding to data of the last meta-analysis of the EBCTCG, for every 4 locoregional recurrences prevented at 5 years, 1 life at 15 years will be saved (LoE 1a). Postmastectomy radiotherapy (PMRT) and regional RT is a standard from tumour stage pT3 and/or pN2a on (LoE 1a). There are increasing data available to advise RT also for patients from pN1a stage on (LoE 1a). The target volumes are under discussion, but quite some arguments exist for comprehensive locoregional RT. There exists, after proper surgery, no indication for irradiation of the axilla (LoE 2a).

Medial tumor location is associated with poorer prognosis. However, the survival outcome of local-regional treatments seems to be not affected by tumor location, arguing that tumor location is not a sufficient indication to modify local-regional treatments in node-negative patients. Local-regional treatment should be based on tumor characteristics and not tumor location. Use of radiation therapy (RT) decreased the 15-year risk of dying from breast cancer from 31% to 26% for patients with negative lymph nodes and from 55% to 48% for patients with positive lymph nodes (LoE 1a).

Rates of local tumour relapse after breast conservation treatment in women with early breast cancer are falling. Explanations for this decline are advances in breast cancer management and aging of the breast cancer population. Breast surgery has become more standardised following publication of practice guidelines and is mostly carried out by specialist surgeons. Systemic therapies (endocrine therapy and chemotherapy) are now more effective and are recommended to a higher proportion of patients than ever before. Significant technical advances in radiotherapy have also been achieved as well as radiotherapy techniques have also improved: CT-based treatment planning, electronic portal imaging devices etc. have improved accuracy and reproducibility of patient set-up, definition and localisation of clinical target volume as well as boost volume, homogeneity of dose distribution and precision of set-up verification. However, due to the lack of data from prospective trials or cohort studies, it is impossible to quantify or judge their impact on local tumor control. Nevertheless, the contributions of each factor are difficult to quantify precisely, but all are likely to be relevant.

Further information (II):

Now, the evidence is strong for survival benefits for both postmastectomy radiation therapy and irradiation after breast conserving surgery. Data from recently published metaanalyses demonstrate conclusively the impact of radiation therapy on local tumor control. Now these data are emerging that even local as well as locoregional relapse has an adverse impact not only for quality of life but also for survival, and substantially affect 15-year

overall mortality. Avoidance of a local recurrence in the remaining breast after BCS as well as avoidance of a locoregional relapse (eg. the thoracic wall or regional lymph nodes) after mastectomy are of comparable relevance to 15-year breast cancer mortality.

New analyses from the SEER and the UZ Brussel data bases provide new evidence for a survival benefit even for the subgroup of pT1-2 pN+ (0-3) breast cancer patients which is in the same range compared with the subgroup of patients with 4 or more pN+: The 15-year OS in the subgroup with ME and ≤ 3 pN+ nodes was 57.0% and 46.6% ($p = 0.0004$) with RT (UZ Brussel) and without RT (SEER), respectively. For BCS and ≤ 3 pN+, the same significant difference in OS at 15 years was seen: 63.8% after RT (UZ Brussel) and 60.4% without RT (SEER; $p = 0.0029$) (Voordeckers M et al. *Strahlenther Onkol* 2009; 185:656-662).

Even more, newest meta-analyses published in 2013 confirm previous results of an update of the EBCTCG Meta-analysis, as presented by S. Darby in December 2009 at the 32nd SABCS, substantially underlining the role of radiation therapy for both locoregional control as well as survival in different subgroups of patients:

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267

Li Y, Moran MS, Huo Q, Yang Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. *PLoS One* 2013;8:e81765.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9. Epub 2013 Oct

Preliminary Note (3/11)

No further information

No references

Postmastectomy Radiotherapy (PMRT) to the Chest Wall (4/11)

Further information and references:

Empfehlungen zur Indikationsstellung zur Postmastektomie-Radiotherapie der Thoraxwand:

New in 2013:

Meta-analyses:

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267

Li Y, Moran MS, Huo Q, Yang Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. *PLoS One* 2013;8:e81765. doi: 10.1371/journal.pone.0081765.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9. Epub 2013 Oct 8.2013

Updated recommendations regarding indication for PMRT of the chest wall even in “intermediate risk” patients:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134)

Biganzoli L, Wildiers H, Oakman C, et al.. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148-60

Recommendations for additional RT of regional lymphatics for patients with 1-3 positive lymph nodes (intermediate risk) in updated guidelines:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer: “with RNI”

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38: “should be discussed on a case by case basis in the multidiscipline team meeting (expert opinion)”

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77: “Young patients should be informed the high local recurrence risk if radiation therapy is avoided....Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion)”

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): strongly recommendation for participation in ongoing clinical trials (SUPREMO). – RT of supraclavicular fossa: “No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement....Participation in clinical trials should be encouraged”.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. *JNCCN* 2013;11:753-761: “1-3 positive lymph nodes: strongly consider radiation therapy to infraclavicular region and supraclavicular area (category 2B). strongly consider radiation therapy to internal mammary nodes (category 2B).” (Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate)

Sautter-Bihl ML, Sedlmayer F, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III: - Radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014;190: in press

Further references:

National Institute for Health and Clinical Excellence UK– (NICE UK) Guidelines:

Harnett A, Smallwood J, Titshall V, Champion A, on behalf of the Guideline Development Group. Practice Guidelines. Diagnosis and treatment of early breast cancer, including locally advanced disease—summary of NICE guidance. *BMJ* 2009;338:b438.

Yarnold Y. Early and locally advanced breast cancer: diagnosis and treatment National Institute for Health and Clinical Excellence guideline 2009. *Clin Oncol (R Coll Radiol)* 2009;21:159-60

National Institute for Health and Clinical Excellence. Early and locally advanced breast cancer: diagnosis and treatment. (Clinical guideline 80.) London: NICE, 2009. www.nice.org.uk/CG80

In node positive patients, the benefit in terms of absolute overall survival is observed in all sub-groups of the meta-analysis. Thus, RT indication is not a subject of debate.

Conversely, the debate is important in sub-groups of N- patients. The rationale for indicating PMRT in N- patients is generally based on the presence of local recurrence risk factors. In the Danish trials, the independent factors influencing survival were: large tumour size, high number of involved nodes +/- extracapsular extent, nodal relapse (supra- or sub-clavicular), less than 2 years interval before the first relapse..

Regarding the updated guidelines for clinical practice from the French expert review board (Belkacemi et al. 2010), the recommendations in N- patients were based on the existence of one or more risk factors for local recurrence such as age (less than 40 years), tumour size (\geq pT3), grade III, multifocality, lymphovascular and/or muscular and/or cutaneous invasion. This is in accordance with the updated Guideline recommendations of the expert group of the German Society of Radiation Oncology (DEGRO) (Wenz et al. 2014, in press) and is not particularly specified in other recently updated guidelines (NCCN 2011; NZGG 2009; Belgian KCE 2013) indicating RT in cases of tumor size >5 cm and close margins (<1 mm) (NCCN 2013).

For the particular cases of T3N0, there is a lack of information and conflicting data. For example, in the USA the majority of practising radiation oncologists recommends PMRT for these tumours. In the study from Taghian et al. (2006) the 10-year recurrence rates were different according to systemic therapy administration (7%) or not (16%). The authors concluded that, in the context of systemic therapy, isolated recurrence rates as first events is lower than 6%. This rate is low enough that the benefit from routine PMRT might not outweigh its potential adverse effects. Controversely as for intermediate risk patients (with 1–3 nodes positive), in whom it has to be demonstrated PMRT provide statistically significant benefit, the lack of randomized trials in T3N0, cannot allow a systematic omission of PMRT.

Further information:

Meta-analyses and randomised clinical controlled trials (RCTs) of locoregional postmastectomy radiation therapy (PMRT) have consistently demonstrated that PMRT reduces the risk of locoregional failure to the chest wall and regional lymphatic drainage sites, including the ipsilateral axillary, supraclavicular and infraclavicular and internal mammary nodes by approximately two-thirds (level I evidence).

In patients with large tumors (pT3 or pT4), R1-/R2-status of tumor resection and four or more involved lymph nodes (pN2), local and locoregional failure (LRF) as first event of disease recurrence remains a clinically significant problem. Regarding these factors, the beneficial worth of PMRT is sufficiently documented and based on high levels of evidence (level 1 evidence) (Jagsi and Pierce 2009). Even patients with an initial T3 or T4 tumor who are treated with primary systemic chemotherapy (i.e. preoperative or neoadjuvant chemotherapy) and subsequently achieve a pCR, still have a high rate of local-regional recurrences and profit from postmastectomy irradiation.

There is little known about the impact of other parameters, e.g. age, influence of EIC and other histopathological factors as well as combination effects. Although PMRT is currently recommended for patients with four or more LN+, there is increasing evidence PMRT may also improve survival rate, which seems to be in the same range for patients with one to three positive lymph nodes or for patients with four or more positive lymph nodes. However, the updated results of the meta-analysis 2006 of the EBCTCG are still unpublished.

For the subgroup of patients with high risk criteria for local recurrence or systemic progression (eg. axillary lymph node-positive premenopausal patients) treated by mastectomy and adjuvant chemotherapy (CMF), PMRT statistically significant reduces isolated locoregional recurrence, distant recurrence, cancer specific deaths, and overall mortality based on the long-term results encompassing a 20-year follow-up. For these patients breast cancer survival is improved with locoregional radiation therapy (Ragaz et al. 2005).

Randomized trials consistently provide evidence for improved outcomes with postmastectomy radiotherapy (PMRT) in high-risk patients (LoE 1a), e.g. node-positive patients with locally advanced breast cancer. The largest absolute reduction in 5-year local relapse probability after radiotherapy was seen for the poor prognosis group. Consequently, PMRT to chest wall and supra-/infraclavicular area should be „strongly considered“ according to the actual guidelines of NCCN (NCCN 2011). In particular, young age continues to evolve as a potentially important risk factor in patients with high-risk features after mastectomy (Garg 2008) (LoE 3b). In contrast to older patients, young patients experience an abnormally high risk of death caused by breast cancer. Among elderly patients, the risk of death from breast cancer does not decrease with increasing age. These facts are important in the discussion of options for adjuvant treatment in patients with breast cancer and in individualising decision whether or not adjuvant treatment should be delivered. Translation of local recurrence reduction into breast cancer mortality reduction after postmastectomy radiotherapy to high-risk breast cancer patients seems to be heterogeneous, with the largest translation occurring within the good prognosis group (Kyndi 2009).

Although nodal status is the major determinant of risk of locoregional relapse (LRR), other factors also contribute, and these assume a greater significance for those with node-negative breast cancer. The role of postmastectomy radiotherapy (PMRT) for lymph node-negative locally advanced breast carcinoma (T3N0M0) after modified radical mastectomy (MRM) with regard to improvement in survival remains an area of controversy. It has been suggested that patients with T3N0 breast cancer represent a favorable subgroup for which PMRT renders little benefit. A retrospective, population-based analysis demonstrated no increase in CSS with PMRT for women with T3N0 breast cancer, lending further support to the hypothesis that T3N0 disease postmastectomy represents a favorable subset of locally advanced breast cancer. The increased OS associated with PMRT in the absence of improved CSS likely reflects patient selection in a nonrandomized dataset. This suggestion is strongly supported in another analysis confirming the use of PMRT for T3N0M0 breast carcinoma after MRM.

PMRT is also highly beneficial in reducing the risk of local recurrence in patients with invasive lobular breast cancer. Local control is excellent for patients with invasive lobular breast cancer who undergo postmastectomy radiotherapy and significantly better than for patients not receiving radiotherapy (LoE 2c) (Poortman et al. 2013, Diepenmaat 2009).

For patients with *stage II breast cancer with one to three positive lymph nodes*, controversy existed about whether radiation therapy as a component of treatment provides a survival benefit. Retrospectively analyzed cohort studies confirm that radiation use was independently associated with improved survival for patients with stage II breast cancer with one to three positive lymph nodes. Because multivariate analyses of retrospective data cannot account for all potential biases, these data required confirmation in randomized clinical trials. In 2013 published data from clinical studies as well as one meta-analysis provided benefits for this subgroup of patients, if PMRT is applied in combination with combination with regional node irradiation (RNI).

In the recent update of the results of the French trial (Hennequin et al. 2013), no difference was observed in terms of control of loco-regional disease or survival between patients that have had IMC RT or not, for inner and central tumours. However, the defenders of systematic RT to the IMC in case of central or internal localisation, in addition to anatomic arguments, suggest that optimising local control by a complete IMC irradiation sterilises the nodal areas to avoid any risk of diffusion from the areas where occult tumour involvement is frequently located. Moreover, the risk of recurrence is probably multiparametric. For Huang et al. (2008) a high risk of IMN metastasis is observed in patients: with $\geq 4N+$, with medial tumour and N+, with T3 tumour and younger than 35 years, with T2 tumour and N+ and patients with T2 and medial tumour (French Guidelines 2010).

Detailed new references:

PMRT in triple negative T1-2 N1-patients:

Chen X, Yu X, Chen J, Yang Z, Shao Z et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with t1-t2 disease and one to three positive lymph nodes after mastectomy. *Oncologist* 2013;18:141-147

PMRT in T1-2 N0-patients:

Hastings J, Iganej S, Huang C, Huang R, Slezak J. Risk factors for locoregional recurrence after mastectomy in stage T1 N0 breast cancer. *Am J Clin Oncol* 2013 Feb 20. [Epub ahead of print]

Truong PT, Sadek BT, Lesperance MF, et al. Is biological subtype prognostic of locoregional recurrence risk in women with pT1-2N0 breast cancer treated with mastectomy? *Int J Radiat Oncol Biol Phys* 2014;88:57-64.

Abi-Raad R, Boutrus R, Wang R, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;81(3):e151-7.

PMRT in T3-N0-patients after primary systemic treatment:

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys* 2014;88:65-72 epub: 2013 Oct 22. pii: S0360-3016(13)03108-8.

Le Scodan R, Selz J, Stevens D, et al. Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. J Radiat Oncol Biol Phys 2012;82:e1-7.

Nagar H, Mittendorf EA, Strom EA, et al. Local-regional recurrence with and without radiation therapy after neoadjuvant chemotherapy and mastectomy for clinically staged T3N0 breast cancer. Int J Radiat Oncol Biol Phys 2011;81:782-7.

PMRT after primary systemic treatment:

Radiotherapy in patients with pathologic response (e.g. ypT0 ypN0) after preoperative chemotherapy and mastectomy

New in 2013/2014:

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 2014;88:65-72 epub: 2013 Oct 22. pii: S0360-3016(13)03108-8. A retrospective trial

Further references:

Bellon JR, Wong JS, Burstein HJ. Should response to preoperative chemotherapy affect radiotherapy recommendations after mastectomy for stage II breast cancer? J Clin Oncol 2012;30:3916-20.

Daveau C, Savignoni A, Abrous-Anane S, et al. Is radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy? Int J Radiat Oncol Biol Phys 2011;79:1452-9.

Le Scodan R, Bruant S, Selz J, et al. [Role of locoregional radiation therapy in breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. The Institut Curie-Hôpital René-Huguenin experience. Cancer Radiother 2011;15:675-82.

Le Scodan R, Selz J, Stevens D, et al. Radiotherapy for stage II and stage III breast cancer patients with negative lymph nodes after preoperative chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 2012;82:e1-7

Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 2012;30:3960-6.

Additional aspect:

Sequencing breast reconstruction and PMRT:

New systematic review in 2013:

Shah C, Kundu N, Arthur D, Vicini F. Radiation therapy following postmastectomy reconstruction: a systematic review. Ann Surg Oncol 2013;20:1313-1322.

Further reference:

Ho A, Cordeiro P, Disa J, et al. Long-term outcomes in breast cancer patients undergoing immediate 2-stage expander/implant reconstruction and postmastectomy radiation. *Cancer* 2012;118:2552-92011.

Overviews 2013/2014

Which patients gain a survival benefit?

Post-mastectomy radiotherapy (PMRT) has shown an absolute overall survival benefit of about 10% in pre- or post-menopausal node positive (N+) patients. Thus, the indications for PMRT are clearly established for the T3–T4 patients and for those presenting with nodal involvement (level 1, grade A) (Belkacemy et al. 2010).

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys* 2013;86:860-866.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. *Eur J Cancer* 2013;49 (Suppl 3): S1 abstract BA2

Impact of mastectomy resection margins

- *If R0 is impossible to reach*

Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. *Breast* 2010;19:14-22

National Comprehensive Cancer Network (NCCN USA) Guidelines: Breast cancer Version: V.3.2013 (<http://www.nccn.org>)

- *PMRT to chest wall for node-negative breast cancer*

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267

Hastings J, Iganej S, Huang C, Huang R, Slezak J. Risk factors for locoregional recurrence after mastectomy in stage T1 N0 breast cancer. *Am J Clin Oncol* 2013 Feb 20. [Epub ahead of print]

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys* 2013;86:860-866.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013;49 (Suppl 3): S1 abstract BA2

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). Int J Radiat Oncol Biol Phys 2014;88:65-72 epub: 2013 Oct 22.

PMRT in lobular breast cancer

Poortmans PM, Bollet M, Van Limbergen E. Infiltrating lobular breast cancer: Truly a separate entity! Consequences for radiation therapy. Radiother Oncol 2013;106:1-4.

Diepenmaat LA, Sangen MJ, Poll-Franse LV, et al. The impact of postmastectomy radiotherapy on local control in patients with invasive lobular breast cancer. Radiother Oncol 2009;91:49-53

PMRT in locally advanced breast cancer

Jagsi R, Pierce L. Postmastectomy radiation therapy for patients with locally advanced breast cancer. Semin Radiat Oncol 2009;19:236-43

PMRT in \geq pN1a (depending on patients' age)

PMRT or – alternatively at minimum – a consultation by a radiation oncologist for discuss PMRT in order to assess individually benefit/risk ratio are also recommended in the updated guidelines of AHS (2013), German Guidelines ((2012), NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2013), NZGG (2009), French Guidelines (2012), SIGN (2013):

References published in 2013 regarding influence of patient's age:

Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on Clinical Management of the Axilla in Older Breast Cancer Patients: A SEER-Medicare Analysis. Ann Surg Oncol [Epub ahead of print] 2013.

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29

Hwang ES, Lichtensztajn DY, Gomez SL, et al. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer 2013;119:1402-11. doi: 10.1002/cncr.27795.

Further references:

Cardoso F, Stordeur S, Vlayen J, et al. Scientific support of the College of Oncology: update of the national guidelines on breast cancer. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2010. KCE Reports 143C. D/2010/10.273/77

Floyd SR, Taghian AG. Post-mastectomy radiation in large node-negative breast tumors: does size really matter? *Radiother Oncol* 2009;91:33-7.

Harnett A, Smallwood J, Titshall V, Champion A, on behalf of the Guideline Development Group. Practice Guidelines. Diagnosis and treatment of early breast cancer, including locally advanced disease—summary of NICE guidance. *BMJ* 2009;338:b438.

National Comprehensive Cancer Network (NCCN USA) Guidelines: Breast cancer Version: V.1.2011 (<http://www.nccn.org>)

New Zealand Guidelines Group. Management of early breast cancer. Wellington: New Zealand Guidelines Group; 2009. or www.nzgg.org.nz

Yarnold Y. Early and locally advanced breast cancer: diagnosis and treatment National Institute for Health and Clinical Excellence guideline 2009. *Clin Oncol (R Coll Radiol)* 2009;21:159-60 (NICE Guidelines)

PMRT in T4

PMRT is also strongly recommended in the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2010/2012), NZGG (2009), French Guidelines (2012), German Guideline (2012)

Sautter-Bihl ML, Souchon R, Budach W, et al. DEGRO Practical Guidelines for radiotherapy of breast cancer II: Postmastectomy radiotherapy, irradiation of regional lymphatics, and treatment of locally advanced disease. *Strahlenther Onkol* 2008;184:347-53

PMRT in patients with invasive cancer if R0 is impossible to reach

PMRT is also strongly recommended in the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2013), NZGG (2009), French Guidelines (2012), German Guideline (2012) and the Guideline of the Netherlands:

Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. *Breast* 2010;19:14-22

Sautter-Bihl ML, Souchon R, Budach W, et al. DEGRO Practical Guidelines for radiotherapy of breast cancer II: Postmastectomy radiotherapy, irradiation of regional lymphatics, and treatment of locally advanced disease. *Strahlenther Onkol* 2008;184:347-53

Special aspect: PMRT in patients with DCIS if R0 is impossible to reach

New in 2013:

Childs SK, Chen YH, Duggan MM, et al. Impact of margin status on local recurrence after mastectomy for ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys* 2013;85:948-52

Fitzsullivan E, Lari SA, Smith B, et al. Incidence and consequence of close margins in patients with ductal carcinoma-in situ treated with mastectomy: is further therapy warranted? Ann Surg Oncol 2013;20:4103-12.

Close margins occur in a minority of patients undergoing mastectomy for DCIS and is the only independent risk factor for LRR. As the LRR rate in patients with close margins is low and less than the rate of contralateral breast cancer, PMRT is not warranted except for patients with multiple close/positive margins that cannot be surgically excised.

PMRT after primary systemic treatment (PST) based on the initial stage prior to PST (cN+, cT3/4a-d)

Identical recommendation regarding this statement by the updated international guidelines (see references on top)

PMRT in young pts with high risk features

Identical recommendation regarding this statement by the updated international guidelines (see references on top)

Updated NCCN-Guidelines: National Comprehensive Cancer Network (NCCN USA) Guidelines: Breast cancer Version: V.3.2013 (<http://www.nccn.org>)

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29

Dragun AE, Huang B, Gupta S, Crew JB, Tucker TC. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. Int J Radiat Oncol Biol Phys 2012;83:e591-6.

Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. J BUON 2012;17:245-8.

van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat 2011;127:207-15

PMRT with additional RT of supra-/infralavicular region in >3 Lnn.

Identical recommendation regarding this statement by the updated international guidelines (see references on top)

Updated NCCN-Guidelines: National Comprehensive Cancer Network (NCCN USA) Guidelines: Breast cancer Version: V.3.2013 (<http://www.nccn.org>)

Further references

Clarke M, Collins R, Darby S, et al, for the Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-2106

Darby S, on Behalf of the Early Breast Cancer Trialists' Collaborative Group University of Oxford, GB. Overview of the randomised trials of radiotherapy in early breast cancer. SABCS 2009; Minisymposium 3, 1. [MS3-1], no full paper version available. Slides of the oral presentation at the 32nd Annual SABCS 2009: www.sabcs.org/

Jagsi R, Pierce L. Postmastectomy radiation therapy for patients with locally advanced breast cancer. *Semin Radiat Oncol* 2009;19:236-43

NCCN (National Comprehensive Cancer Network). Clinical Practice Guidelines in Oncology: Breast Cancer - Version V.3.2013

Indications for PMRT are independent of adjuvant systemic treatment

Identical recommendation regarding this statement by the updated international guidelines (see references on top)

Updated NCCN-Guidelines: National Comprehensive Cancer Network (NCCN USA) Guidelines: Breast cancer Version: V.3.2013 (<http://www.nccn.org>)

New in 2013:

Shim SJ, Park W, Huh SJ, et al. The role of postmastectomy radiation therapy after neoadjuvant chemotherapy in clinical stage II-III breast cancer patients with pN0: a multicenter, retrospective study (KROG 12-05). *Int J Radiat Oncol Biol Phys* 2014;88:65-72 epub: 2013 Oct 22. pii: S0360-3016(13)03108-8.

In a retrospective trial including 151 patients with mastectomy presenting ypN0 status after NAC, 105 received PMRT and 46 did not. There were no differences regarding 5-year DFS, LRR and OS, respectively. The authors concluded that PMRT might not be necessary for ypN0 patients after NAC. Nevertheless, prospective randomized studies are warranted to assess, whether PMRT might be safely omitted for a subgroup of patients after NAC and mastectomy resulting in ypN0.

This issue is now addressed in the Maastricht Radiation Oncology – register trial: Radiotherapy After Primary Chemotherapy for Breast Cancer (RAPCHEM) trial (NCT01279304).

RT of the Breast after Breast Conservig Surgery in Invasive Carcinoma (5/11)

Further information and references:

Radiation therapy of the breast in addition to breast conserving surgery - whatever the extent of partial surgery - is strongly recommended in the updated guidelines of Alberta Health System (2013), NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2013), NZGG (2009), German (2012), Scottish Intercollegiate Guidelines Network (SIGN 2013), French expert review boards (2011), The Netherlands (2012). It reduces the risk of relapse in all patient sub-groups (LoE 1A):

New

Whole breast irradiation (WBI) 1a A ++

Updated guideline recommendation in favor of RT following BCS:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38

Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, Gentilini O, Peccatori F, Fourquet A, Delaloge S, Marotti L, Penault-Llorca F, Kotti-Kitromilidou AM, Rodger A, Harbeck N; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29.

Goldhirsch A, Wiener EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer. Ann Oncol 2013;24:2206-2223

Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol 2013;14:1086-1094

See comment in: Haffty BG, Buchholz TA: Hypofractionated breast radiation: preferred standard of care? Lancet Oncol 2013;14:1032-1034

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013.

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

National Cancer Institute USA, updated 11/19/2013

Nielsen MH, Berg M, Pedersen AN, et al; Danish Breast Cancer Cooperative Group Radiotherapy Committee. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. *Acta Oncol* 2013;52:703-10

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134)

Sedlmayer F, Sautter-Bihl ML, Budach W, Dunst J, Fastner G, Feyer P, Fietkau R, Haase W, Harms W, Souchon R, Wenz F, Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. *Strahlenther Onkol* 2013;189:825-833

Mammacarcinoom. Landelijke richtlijn, Versie: 2.0. Datum Goedkeuring: 13-02-2012. Richtlijn Mammacarcinoom. Evidenced-based Guideline 13.02.2012: www.oncoline.nl/mammacarcinoom.

Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. 3. Auflage: Aktualisierung 2012. Zuckschwerdt Verlag, 2012 ISBN: 978-3-86371-073-6

Besnard S, Cutuli B, Fourquet A, Giard S, Hennequin C, Leblanc-Onfroy M, Mazeau-Woynar V, Verdoni L. Radiothérapie du cancer du sein infiltrant: recommandations nationales françaises [Radiotherapy of invasive breast cancer: French national guidelines] *Cancer Radiother* 2012;16:503-513 French.

Cutuli B. [Radiotherapy for breast cancer: Which strategy in 2012?]. *Cancer Radiother* 2012;16:493-502

Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148-60

New in 2013:

Hypofractionation for WBI: 1a B ++*

Hypofractionated (hf) radiotherapy is safe and effective at 10-year follow-up. A lower total radiation dose given in fewer slightly larger fractions and delivered over a shorter period of time was as safe and effective as the standard five-weeks schedule of radiotherapy. Of note: Most patients included in the hypofractionation RCT received a sequential boost to the tumor bed following WBI!

Nevertheless, the issue of fractionation of RT of the whole breast is still a subject of discussion in international societies of radiation oncology (ASTRO, NICE, ESTRO, DEGRO, French expert review board). Regarding hypofractionated WBI, new data from RCT are convincing and gave reason to state that hypofractionated radiation therapy should be the new standard in selected patients. Therefore, hypofractionated radiation therapy schemes are considered in updated guidelines.

It is important to keep in mind that the impact of HF on late cardiac toxicity is not yet evaluated beyond ten years [Whelan et al. 2010; Haviland et al. 2013]; as the latency for clinical manifestation of cardiovascular effects is 15 years or longer, HF might turn out to be critical in cases of relevant dose exposure to the heart, especially in women with a longer life expectancy.

Updated (guideline) recommendations in favor of hypofractionation as alternative fractionation regime for RT following BCS:

Cardoso F, Loibl S, Pagani O, et al. ; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. “has to be considered with caution!”

Goldhirsch A, Wiener EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: Highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer. Ann Oncol 2013;24:2206-2223

Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists’ Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. Lancet Oncol 2013;14:1086-1094 Hypofractionation is the new standard in UK

See comment in: Haffty BG, Buchholz TA: Hypofractionated breast radiation: preferred standard of care? Lancet Oncol 2013;14:1032-1034

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013.

http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “shorter fractionation schedules should be considered”.

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-833 „Hypofractionated WBI with single doses up to 2.7 Gy ...to total doses of 40-42,5 Gy is an option for older women with pT1-2 pN0 who need no chemotherapy“

2012:

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Besnard S, Cutuli B, Fourquet A, Giard S, Hennequin C, Leblanc-Onfroy M, Mazeau-Woynar V, Verdoni L. Radiothérapie du cancer du sein infiltrant: recommandations nationales françaises [Radiotherapy of invasive breast cancer: French national guidelines] Cancer Radiother 2012;16:503-513 French.

Cutuli B. [Radiotherapy for breast cancer: Which strategy in 2012?]. Cancer Radiother 2012;16:493-502

Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012;13:e148-60

Herbert C, Nichol A, Olivetto I, Weir L, Woods R, Speers C, Truong P, Tyldesley S. The impact of hypofractionated whole breast radiotherapy on local relapse in patients with grade 3 early breast cancer: a population-based cohort study. Int J Radiat Oncol Biol Phys 2012;82:2086-92

Boost-irradiation (improves local control) 1a A +

Updated guideline recommendation in favor of boost to tumor bed following WBI BCS:

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38 “can be offered to patients at high risk”.

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. JNCCN 2013;11:753-761: “recommended in patients at higher risk”.

National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “recommended in all patients aged 50 years or under 50 year at diagnosis and should be considered in patients over 50 years, especially those with high grade cancer”

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-833: „A boost in addition to WBI reduces local recurrence in all age groups and should therefore be offered to patients who appear biologically and mentally fit enough to experience the benefit of improved local control”

“For the remaining patients especially when they are >60 years with small, node - negative, hormone receptor-positive tumors, omission of a boost may be considered”.

“Regarding SIB techniques within normofractionated WBI, single tumor bed doses of 2.1 Gy for low-risk tumors up to 2.25 Gy for constellations with higher risk of local recurrence seem to be within the acceptable range.”

Boost-RT to the tumor (region) prior versus after BCS:

Van der Leij F, Elkhuisen PH, Janssen TM. External beam partial breast irradiation: difference in pre- and postoperative target volume delineation. Radiother Oncol 2012;103:S250. *In consequence: PAPBI-Trial = Preoperative Accelerated Partial Breast Irradiation (PAPBI) using cone-beam technique in preop APBI-Boost-RT! (NCT01024582-Phase II-trial). Op 6 Wochen nach PAPBI!*

Short course RT with simultaneous integrated boost-RT: 2a C +/-

New in 2013:

Freedman GM, White JR, Arthur DW, Li XA, Vicini FA. Accelerated fractionation with a concurrent boost for early breast cancer. Radiother Oncol 2013;106:15-20

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Is the simultaneously integrated boost (SIB) technique for early breast cancer ready to be adopted for routine adjuvant radiotherapy? Statement of the German and the Austrian Societies of Radiooncology (DEGRO / ÖGRO). Strahlenther Onkol 2013;189:193-196

2012:

Freedman GM, Anderson PR, Bleicher RJ, Litwin S, Li T, Swaby RF, Ma CM, Li J, Sigurdson ER, Watkins-Bruner D, Morrow M, Goldstein LJ. Five-year local control in a phase II study of hypofractionated intensity modulated radiation therapy with an incorporated boost for early stage breast cancer. Int J Radiat Oncol Biol Phys 2012;84:888-93.

Hurkmans CW, Dijckmans I, Reijnen M, et al. Adaptive radiation therapy for breast IMRT-simultaneously integrated boost: three-year clinical experience. *Radiother Oncol* 2012;103:183-7

Scorsetti M, Alongi F, Fogliata A, Pentimalli S, Navarria P, Lobefalo F, Garcia-Etienne C, Clivio A, Cozzi L, Mancosu P, Nicolini G, Vanetti E, Eboli M, Rossetti C, Rubino A, Sagona A, Arcangeli S, Gatzemeier W, Masci G, Torrasi R, Testori A, Alloisio M, Santoro A, Tinterri C. Phase I-II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: a report of feasibility and early toxicity results in the first 50 treatments. *Radiat Oncol* 2012;7:145.

Van Parijs H, Miedema G, Vinh-Hung V, Verbanck S, Adriaenssens N, Kerkhove D, Reynders T, Schuermans D, Leysen K, Hanon S, Van Camp G, Vincken W, Storme G, Verellen D, De Ridder M. Short course radiotherapy with simultaneous integrated boost for stage I-II breast cancer, early toxicities of a randomized clinical trial. *Radiat Oncol* 2012;7:80.

APBI / IORT as sole radiotherapeutic modality in comparison to WBI:

New in 2013:

Aristei C, Palumbo I, Capezzali G, et al. Outcome of a phase II prospective study on partial breast irradiation with interstitial multi-catheter high-dose rate brachytherapy. *Radiother Oncol* 2013;108:236-241

Krengli M, Calvo FA, Sedlmayer F, et al. Clinical and technical characteristics of intraoperative radiotherapy: Analysis of the ISORT-Europe database. *Strahlenther Onkol* 2013;189:729-737.

Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. Accelerated partial breast irradiation with intraoperative electrons: Using GEC-ESTRO recommendations as guidance for patient selection. *Radiother Oncol* 2013;106:21-7

Polgar C, Fodor J, Major T, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: Ten-year results of the Budapest randomized trial. *Radiother Oncol* 2013;108:197-202

Stewart AJ, Hepel JT, O'Farrell DA, Devlin PM, Price LL, Dale RG, Wazer DE. Equivalent uniform dose for accelerated partial breast radiation using the MammoSite applicator. *Radiother oncol* 2013;108:232-235

Tuschy B, Berlit S, Nasterlack C, et al. Intraoperative radiotherapy of early breast cancer using low-kilovoltage x-rays - reasons for omission of planned intraoperative irradiation. *Breast J* 2013;19:325-8

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M; on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative

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Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Rotmensz N, Sangalli C, Luini A, Veronesi U, Orecchia R. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. Int J Radiat Oncol Biol Phys 2012;83:806-13.

IORT administered as anticipated boost radiation therapy during breast conserving surgery followed by whole breast irradiation

Bartelink H, Bourcier C, Elkhuzen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? Radiother Oncol 2012;104:139-42

2012:

Azoury F, Heymann S, Acevedo C, et al. Phase II trial of 3D-conformal accelerated partial breast irradiation: lessons learned from patients and physicians' evaluation. Radiother Oncol 2012;103:193-8

Bartelink H, Bourcier C, Elkhuzen P. Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic? Radiother Oncol 2012;104:139-42

Ferraro DJ, Garsa AA, DeWees TA, Margenthaler JA, Naughton M, Aft R, Gillanders WE, Eberlein T, Matesa MA, Zoberi I. Comparison of accelerated partial breast irradiation via multicatheter interstitial brachytherapy versus whole breast radiation. Radiat Oncol 2012;7:53.

Formenti SC, Hsu H, Fenton-Kerimian M, et al. Prone accelerated partial breast irradiation after breast-conserving surgery: five-year results of 100 patients. Int J Radiat Oncol Biol Phys 2012;84:606-11

Technical aspects / new techniques regarding delivery of RT, in particular delivery APBI / IMRT, and toxicity regarding simultaneous integrated boost radiotherapy (SIB)

New in 2013:

Appelt AL, Vogelius IR, Bentzen SM. Modern hypofraction schedules for tangential whole breast irradiation decrease the fraction size-corrected dose to the heart. Clin Oncol (R Coll Radiol) 2013;25:147-25.doi: 10.1016/j.clon.2012.07.012

Bantema-Joppe EJ, Vredevelde EJ, de Bock G, et al. Five years outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence. *Radiother Oncol* 2013;108:269-272

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RT-field size / planned target volume in SN+, cN0 breast cancer without axillary dissection

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Long-term cosmesis WBI +/- boost

Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, van der Hulst-Vijgen MH, Noordijk EM, Poortmans PM, Rodenhuis CC, Struikmans H. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol 2012;23:2591-8: *A boost dose worsens the change in breast appearance in the first 3 years. Moreover, the development of fibrosis associated with whole-breast irradiation, as estimated with the relative asymmetry features, is an ongoing process until (at least) 9 years after irradiation.*

Long-term cosmesis WBI +/- boost

Immink JM, Putter H, Bartelink H, Cardoso JS, Cardoso MJ, van der Hulst-Vijgen MH, Noordijk EM, Poortmans PM, Rodenhuis CC, Struikmans H. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. Ann Oncol 2012;23:2591-8

The impact of age on outcome in early-stage breast cancer

Albert JM, Liu DD, Shen Y, Pan IW, Shih YC, Hoffman KE, Buchholz TA, Giordano SH, Smith BD. Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery. *J Clin Oncol* 2012;30:2837-43.

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Sautter-Bihl ML, Sedlmayer F, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Rödel C, Souchon R, Wenz F, Sauer R. When are breast cancer patients old enough for the quitclaim of local control? *Strahlenther Onkol* 2012;188:1069-73

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Boost-RT and hypofractionation on outcome in DCIS

Wai ES, Lesperance ML, Alexander CS, Truong PT, Culp M, Moccia P, Lindquist JF, Olivotto IA. Effect of radiotherapy boost and hypofractionation on outcomes in ductal carcinoma in situ. *Cancer* 2011;117:54-62

Areas of uncertainty, but, however, with improving data in favour radiation therapy:

- Survival benefit in stage II patients with one to three positive lymph nodes
- Impact of radiotherapy of the locoregional lymphatics in pN1a (1-3 positive nodes)
- Best approach after a microscopically incomplete tumor resection in a breast conserving strategy
- Properly definition of patient subgroups, with a low risk for a local relapse after complete surgical tumor removal or after radiotherapy by use of lower dose and /smaller volume concepts
- Shortening RT course by use of hypofractionation concepts

Further references

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Special aspects

Systematic review

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Effect of resection margin status on local relapse after BCS and RT in DCIS:

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Combined effects of systemic therapy and RT on local relapse rates

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Whole breast irradiation (WBI) 1a A ++

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Hypofractionation schedules for WBI: 1a A ++*

See: New data of RCT published in 2012 listed above!

The authors of the Cochrane Collaboration Breast Cancer Group have also reviewed (2010) the data of the RCT dealing with hypofractionated schemes altering their conclusion of the last review from 2008 substantially stating „Two new studies have been published since the last version of the review, altering our conclusions. “We have evidence from four low to medium quality randomised trials that using unconventional fractionation regimens (greater than 2 Gy per fraction) does not affect local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance or late toxicity for selected women treated with breast conserving therapy. These are mostly women with node negative tumours smaller than 3 cm and negative pathological margins“. Nevertheless, caution is still warranted because long-term follow up (>5 years) is available for only a small proportion of the patients randomised. Longer follow up is required for a more complete assessment of the effect of altered fractionation.

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Partial breast irradiation (PBI) - No long term follow up! Only as part of prospective trials!

New:

ASTRO Consensus Panel Guideline:

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Boost-irradiation (improves local control)

Following whole breast irradiation boost RT of the tumor bed is recommended in the updated guidelines of NCCN USA (2012), NICE CG80 (2009), Belgian KCE (2010), NZGG (2009), French Guidelines (2012):

In the updated guidelines of NCCN USA (2012), NICE CG80 (2009), Belgian KCE (2012), NZGG (2009), French expert review board (2012) as well as in guidelines of other expert groups delivery of a boost of 10–16 Gy to the tumour bed following whole breast irradiation is recommended based on the results of three RCT showing the importance of an increase in the dose to the tumour bed in order to improve local control (LoE 1A). Updated data from the EORTC trial have confirmed this advantage for patients of all ranges of ages, including those over 60 years of age. For older patients (>70 years) the decision to deliver the boost should be discussed taking in consideration individual factors, i.e. the tumour size, extent of

surgical margins and a possible presence of a large extensive in situ component as well as grade. The surgical clips marking the original tumour bed should indicate the borders of the excision particularly in the case of oncoplastic remodelling procedures.

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Absolute benefit depending on patient's age

Antonini N, Jones H, Horiot JC, al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007;82:265-71

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Dose-effect relationship independent of pts.' age

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Boost-irradiation in node-negative tumors, endocrine responsive, complete resection

Updated NCCN guideline recommends boost to the tumor bed in patients being at higher risk for local failure (age <50, positive axillary nodes, lymphovascular invasion, or close margins) (NCCN 2012). French guideline supports individual discussion and decision making keeping in mind individual factors for elderly patients (Belkacemi et al. 2010). For patients received hyperfractionated WBI boost RT should be conventional fractionated, i.e. 1.8-2.0 Gy per fraction.

Belkacémi Y, Fourquet A, Cutuli B, Bourcier C, Hery M, Ganem G, Marsiglia H, Namer M, Gligorov J, Azria D. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. *Crit Rev Oncol Hematol* 2010 Jul 6. [Epub ahead of print]

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Boost RT after BCS in Invasive Carcinoma (6/11)

Further information and references:

Boost-Radiotherapie der Tumorregion nach brusterhaltender operativer Therapie:

Boost-irradiation (improves local tumor control) Ia A +

Updated guideline recommendation in favor of boost to tumor bed following WBI after BCS:

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38 “can be offered to patients at high risk”.

Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur J Cancer 2012;48:3355-77. doi: 10.1016/j.ejca.2012.10.004. Epub 2012 Oct 29.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. JNCCN 2013;11:753-761: “recommended in patients at higher risk”.

National Cancer Institute USA, updated 11/19/2013

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): “recommended in all patients aged 50 years or under 50 year at diagnosis and should be considered in patients over 50 years, especially those with high grade cancer”

Sedlmayer F, Sautter-Bihl ML, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer I : Radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol 2013;189:825-833: „A boost in addition to WBI reduces local recurrence in all age groups and should therefore be offered to patients who appear biologically and mentally fit enough to experience the benefit of improved local control”

“For the remaining patients especially when they are >60 years with small, node - negative, hormone receptor-positive tumors, omission of a boost may be considered”.

“Regarding SIB techniques within normofractionated WBI, single tumor bed doses of 2.1 Gy for low-risk tumors up to 2.25 Gy for constellations with higher risk of local recurrence seem to be within the acceptable range.”

Hypofractionation and sequential boost:

No increased toxicity has been observed in START A and START B-trials.

Haviland JS, Owen R, Dewar J, et al., on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of hypofractionating for treatment of early breast cancer: 10-year follow-up results of two randomized controlled trials. *Lancet Oncol* 2013;14:1086-1094

See comment in: Haffty BG, Buchholz TA: Hypofractionated breast radiation: preferred standard of care? *Lancet Oncol* 2013;14:1032-1034

Whole breast radiation with simultaneous integrated boost-RT

Freedman GM, White JR, Arthur DW, et al. Accelerated fractionation with a concurrent boost for early breast cancer. *Radiother Oncol* 2013;106:15-20

Mukesh MB, Harris E, Collette S, et al. Normal tissue complication probability (NTCP) parameters for breast fibrosis: pooled results from two randomised trials. *Radiother Oncol* 2013;108:293-8

IOERT as anticipated boost prior WBI:

Fastner G, Sedlmayer F, Merz F, et al. on behalf of the ISIORT Europe. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT Pooled Analysis. *Radiother Oncol* 2013; 108:279-86

Improved local tumor control:

Absolute benefit depending on patient's age

In the updated guidelines of NCCN USA (2013), NICE CG80 (2009), Belgian KCE (2012), NZGG (2009), French expert review board (2012) delivery of a boost of 10–16 Gy to the tumour bed following whole breast irradiation is recommended based on the results of three RCT showing the importance of an increase in the dose to the tumour bed in order to improve local control (LoE 1A). Updated data from the EORTC trial have confirmed this advantage for patients of all ranges of ages, including those over 60 years of age. For older patients (>70 years) the decision to deliver the boost should be discussed taking in consideration individual factors, i.e. the tumour size, extent of surgical margins and a possible presence of a large extensive in situ component as well as grade. The surgical clips marking the original tumour bed should indicate the borders of the excision particularly in the case of oncoplastic remodelling procedures.

Intraoperative RT as anticipated boost radiotherapy

Fastner G, Sedlmayer F, Merz F, et al. on behalf of the ISIORT Europe. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT Pooled Analysis. *Radiother Oncol* 2013; 108:279-86

Vaidya JS, Baum M, Tobias JS, et al. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011;81:1091-7

Long-term cosmesis WBI +/- boost

Immink JM, Putter H, Bartelink H, et al. Long-term cosmetic changes after breast-conserving treatment of patients with stage I-II breast cancer and included in the EORTC 'boost versus no boost' trial. *Ann Oncol* 2012;23:2591-8: A boost dose worsens the change in breast appearance in the first 3 years. Moreover, the development of fibrosis associated with whole-breast irradiation, as estimated with the relative asymmetry features, is an ongoing process until (at least) 9 years after irradiation.

Dose-effect relationship independent of pts.' age

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Poortmans PM, Collette L, Bartelink H, Struikmans H, et al.; EORTC Radiation Oncology and Breast Cancer Groups. The addition of a boost dose on the primary tumour bed after lumpectomy in breast conserving treatment for breast cancer. A summary of the results of EORTC 22881-10882 "boost versus no boost" trial. *Cancer Radiother* 2008;12:565-70.

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Poortmans P. Evidence based radiation oncology: breast cancer. *Radiother Oncol* 2007;84:84-101

Further information

Regarding local tumor control in breast-conserving treatment, radiation therapy is required (LOE 1a). There exists a dose-effect relationship, which is independent of patients' age (LOE 1b).

Additional boost-RT is able to reduce the local recurrence rate significantly in every age group with most benefit for young patients. With a median follow up of 10 years, boost RT could not be demonstrated to have an impact on survival rate (LOE 1b).

Actual published 10-year results of the randomised EORTC Trial 22881-10882 'boost versus no boost' confirmed:

Increase of the dose with 16 Gy after whole breast irradiation (WBI) delivered as boost radiotherapy confined to the tumor bed, is associated with an improved local control for patients after a complete lumpectomy only. Up till now, with 10 years median follow-up, no impact on survival was observed (LOE 1b).

There was no statistically significant difference in local control or survival between the high boost dose of 26 Gy and the low boost dose of 10 Gy in patients with microscopically incomplete excision of early breast cancer.

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Statement: Improved local tumor control

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Poortmans PM, Collette L, Horiot JC, et al.; on behalf of the EORTC Radiation Oncology and Breast Cancer Groups. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol 2009;90:80-85.

Poortmans P. Evidence based radiation oncology: breast cancer. Radiother Oncol 2007;84:84-101

Statement: All ages: LRR reduction ($12 \geq 7\%$)

Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. Radiother Oncol 2007;82:265-71

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Poortmans P. Evidence based radiation oncology: breast cancer. Radiother Oncol 2007;84:84-101

Statement: <40 years: LRR reduction ($29 \geq 10\%$)

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Statement: high grade invasive ductal cancer

Jones HA, Antonini N, Hart AA, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC Boost Versus No Boost Trial. J Clin Oncol 2009;27:4939-47

Statement: Additional boost RT does not impact survival

Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007;82:265-71

Bartelink H, Horiot J-C, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25:3259-65

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Radiotherapy of the Axilla (7/11)

Further information and references:

Indikationsstellung zur Radiotherapie der Axilla

Neu 2013:

Radiation therapy of regional lymphatics

Bourgier C, Aimard L, Bodez V, et al. Adjuvant radiotherapy in the management of axillary node negative invasive breast cancer: A qualitative systematic review. Crit Rev Oncol Hematol 2013;86:33-41

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Chang JS, Park W, Kim YB, et al. Long-term survival outcomes following internal mammary node irradiation in stage II-III breast cancer: results of a large retrospective study with 12-year follow-up. Int J Radiat Oncol Biol Phys 2013;86:867-72.

Courdi A, Chamorey E, Ferrero J-M, et al. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. Radiother Oncol 2013;108:259-265.

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. Int J Radiat Oncol Biol Phys 2013;86:860-866.

Jagsi R, Pierce L. Radiation therapy to the internal mammary nodal region in breast cancer: the debate continues. Int J Radiat Oncol Biol Phys 2013;86:813-815

Karam I, Lesperance MF, Berrang T, et al. pN0(i+) Breast Cancer: Treatment Patterns, Locoregional Recurrence, and Survival Outcomes. Int J Radiat Oncol Biol Phys 2013;87:731-737.

Kim SI, Cho SH, Lee JS, et al. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. Br J Cancer 2013;109:1165-71.

Liu D, Chen Y, Deng M, Xie G, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9. doi: 10.1007/s12282-013-0497-8. Epub 2013 Oct 8.2013

Abstract

Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.

Offersen BV, Nielsen HM, Overgaard M, Overgaard J. Is regional nodes radiotherapy an alternative to surgery? *Breast* 2013;22 Suppl 2:S118-28. doi: 10.1016/j.breast.2013.07.023.

Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. *Eur J Cancer* 2013;49 (Suppl 3): S1 abstract BA2

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RT-field size/ planned target volume in SN+, cN0 breast cancer without axillary dissection

Milgrom S, Cody H, Tan L, et al. Characteristics and outcomes of sentinel node-positive breast cancer patients after total mastectomy without axillary-specific treatment. Ann Surg Oncol 2012;19:3762-70

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Prognostic factors after BCS in young patients

van der Sagen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat 2011;127:207-15

Vestjens JH, de Boer M, van Diest PJ, et al. Prognostic impact of isolated tumor cells in breast cancer axillary nodes: single tumor cell(s) versus tumor cell cluster(s) and microanatomic location. Breast Cancer Res Treat 2012;131:645-51.

Werkhoven E, Hart G, Tinteren H, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. Radiother Oncol 2011;100:101-7

Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis. JAMA 2011;305:569-75.

Haffty BG, Hunt KK, Harris JR, Buchholz TA. Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. J Clin Oncol 2011;29:4479-81.

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Whelan TJ, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol* 2011;29: suppl; abstr LBA1003

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (8/11)

Further information and references:

Indikationsstellung zur Radiotherapie weiterer lokoregionaler Lymphabflussregionen

Neu 2013:

Metaanalysen:

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267: additional regional lymph nodes irradiation of medial supraclavicular and internal mammary for patients with positive axillary sentinel nodes provide statistically significant benefits regarding disease-free survival, distant metastases-free survival and overall survival, respectively

Li Y, Moran MS, Huo Q, Yang Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. *PLoS One* 2013;8:e81765. doi: 10.1371/journal.pone.0081765.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9. doi: 10.1007/s12282-013-0497-8. Epub 2013 Oct 8.2013

Recommendations in updated guidelines:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer: “with RNI”

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38: “should be discussed on a case by case basis in the multidiscipline team meeting (expert opinion)”

Cardoso F, Loibl S, Pagni O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77: “Young patients should be informed the high local recurrence risk if radiation therapy is avoided....Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion)”

Sautter-Bihl ML, Sedlmayer F, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III: - Radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014;190: in press

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): strongly recommendation for participation in ongoing clinical trials (SUPREMO). – RT of supraclavicular fossa: “No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement....Participation in clinical trials should be encouraged”.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. *JNCCN* 2013;11:753-761: “1-3 positive lymph nodes: strongly consider radiation therapy to infraclavicular region and supraclavicular area (category 2B). strongly consider radiation therapy to internal mammary nodes (category 2B).” (Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate)

Further references:

Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on Clinical Management of the Axilla in Older Breast Cancer Patients: A SEER-Medicare Analysis. *Ann Surg Oncol* 2013;20:4145-52

Chang JS, Park W, Kim YB, et al. Long-term survival outcomes following internal mammary node irradiation in stage II-III breast cancer: results of a large retrospective study with 12-year follow-up. *Int J Radiat Oncol Biol Phys* 2013;86:867-72.

Courdi A, Chamorey E, Ferrero J-M, et al. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. *Radiother Oncol* 2013;108:259-265.

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. *Int J Radiat Oncol Biol Phys* 2013;86:860-866.

Jagsi R, Pierce L. Radiation therapy to the internal mammary nodal region in breast cancer: the debate continues. *Int J Radiat Oncol Biol Phys* 2013;86:813-815

Karam I, Lesperance MF, Berrang T, et al. pN0(i+) Breast Cancer: Treatment Patterns, Locoregional Recurrence, and Survival Outcomes. *Int J Radiat Oncol Biol Phys* 2013;87:731-737.

Kim SI, Cho SH, Lee JS, et al. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. *Br J Cancer* 2013;109:1165-71.

Offersen BV, Nielsen HM, Overgaard M, Overgaard J. Is regional nodes radiotherapy an alternative to surgery? *Breast* 2013;22 Suppl 2:S118-28. doi: 10.1016/j.breast.2013.07.023.

Abstract

Sentinel node biopsy (SN) in breast cancer treatment was introduced in the mid-1990s in order to be able to stage patients before decision of definitive surgery. Since then, both the pathological examinations of the SN and the systemic adjuvant treatment have improved and cause new challenges in the correct decision making regarding whether or not to radically treat the axilla in case of a positive SN. In SN positive patients, current St. Gallen guidelines support no completion ALND (axillary lymph node dissection) in clinically node-negative patients with 1-2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy (RT). ALND is being questioned due to increased morbidity compared with SN biopsy alone, and to limited long term benefit on disease free survival in selected patients. An alternative to ALND is treating the axilla with nodal RT although this treatment is mostly used as adjuvant treatment after ALND in high risk patients. Few studies have investigated the benefit of nodal RT compared to ALND, and no consensus has yet been reached. Clinical decision making regarding treating the axilla should be based on relevant data, and in this review studies aiming at deciding whether or not and how the axilla should be treated in SN positive patients will be discussed. Furthermore treatment choice will be discussed, since besides ALND, both breast irradiation and nodal irradiation might cure residual disease after SN. Also the issue of improved systemic adjuvant treatment will be discussed in relation to eventually no regional axillary treatment.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013;49 (Suppl 3): S1 abstract BA2

Rutgers EJ, Donker M, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial (10981/22023. J Clin Oncol 2013;31,Abstract LBA1001.

Guidelines 2012 / recommendations 2012 for irradiation of the locoregional lymphatics

a) Mammacarcinoom. Landelijke richtlijn, Versie: 2.0. Datum Goedkeuring: 13-02-2012. Richtlijn Mammacarcinoom. Evidenced-based Guideline 13.02.2012: www.oncoline.nl/mammacarcinoom.

b) Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. 3. Auflage: Aktualisierung 2012. Zuckschwerdt Verlag, 2012 ISBN: 978-3-86371-073-6

c) Besnard S, Cutuli B, Fourquet A, et al. Radiothérapie du cancer du sein infiltrant: recommandations nationales françaises [Radiotherapy of invasive breast cancer: French national guidelines.] Cancer Radiother 2012;16:503-513 French.

Cutuli B. [Radiotherapy for breast cancer: Which strategy in 2012?]. Cancer Radiother 2012;16:493-502

e) Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148-60

f) National Comprehensive Cancer Network (NCCN USA) Guidelines: NCCN-Practice Guidelines - Breast cancer Version: V.3.2012 (<http://www.nccn.org>)

Further information:

For patients with breast cancer ipsilateral lymph edema of the arm, restriction of shoulder motion as well as brachial plexopathy are relevant functional treatment sequelae correlated with treatment modality which also have a strong negative influence on the quality of life. Specific morbidity of surgical (e.g. extent of the axillary dissection, length of the scar) and radiotherapeutic (radiation following surgery, radiation without previous surgery) treatment as well as individual host factors may influence functional outcome. Axillary dissection provides sufficient information on nodal status being clinically a major prognostic factor. Nonetheless, axillary node dissection is responsible for functional sequelae which might be enhanced by additional postoperative irradiation of the axilla (with or without additional irradiation of ipsilateral supraclavicular lymph nodes). Local treatment sequelae are mainly an arm edema, swelling of the arm caused by lymphostasis, functional reduction of ipsilateral shoulder joint responsible for consecutive impairment in shoulder movement as well as other motoric and neurological deficits. With the sentinel lymph node biopsy (SNB) this aspect of reducing the adverse postsurgical treatment effects in the shoulder-arm-area is already taken into account from operative side. Regarding percutaneous irradiation there exist also differentiated indicators for postoperative radiation therapy for the treatment of the regional lymphatics. The recommendations about the irradiation of the regional lymph nodes are internationally still mixed since, up to now, the validation of the radiotherapeutic effects in retrospective studies are as yet inadequate and current international prospective studies including large numbers of patients are not yet completed.

Current studies prospectively examined whether the sentinel node biopsy is as effective as the axillary lymph node dissection. Concordance rates between 97-100% and a rate of false negative SNB reports of 0-10% have been specified so far. The alternative of an axilla-irradiation as well as the irradiation of the additional regional lymphatics has as yet been validated, but the results are still pending. At present international studies regarding this subject are being carried out. In detail these are the SUPREMO-phase III-trial/EORTC-trial; EORTC-Protocol 22922-10925; EORTC-Protocol 22023-10981(AMAROS)-trial, NSABP-B32-trial (negative SN- and axillary node status respectively). A negative SNB status means that no further operative therapy is necessary and that there is no need for adjuvant radiation therapy of the regional lymph nodes; a positive SNB however justifies further adjuvant therapy-measures (Kuehn et al. 2004). The meaning of micrometastases detected in the SNB is unclear (Leidenius et al. 2005). Without any further axillary dissection in case of a positive SNB status the irradiation of the axilla offers a therapeutic alternative. Whether it is an equivalent alternative to surgery and whether there exists an equivalence of both therapy modalities has not been sufficiently clarified yet and should be examined in randomized interdisciplinary studies. Retrospectively the irradiation of the axilla achieves a local control which is just as good as the sole axillary dissection, nonetheless, with reduced functional treatment sequelae regarding axilla, shoulder and arm (Louis-Sylvestre et al. 2004).

The irradiation of the axilla is currently recommended for patients presenting extended lymph node involvement (>3 affected lymph nodes; pN2a) and with contraindication or omission of a sufficient operative exploration of the armpit. However the extracapsular nodal tumor extension of axillary node metastases is prognostical judged controversially as well as the indication derived from with regard to a need for axillary node irradiation (Gruber et al. 2008; Stranzl et al. 2004). However, the indication for radiotherapy has to be considered individually and should include further factors, e.g. the extent of the axillary lymph node dissection and the number of affected nodes. An irradiation of the regional undissected lymph nodes therefore appears to be appropriate in case of locally advanced breast cancer, extended involvement of the axillary nodes, especially with additional extracapsular tumor extension, with inadequate surgical removal of axillary lymph nodes, contraindication or the refusal of an axillary dissection. However, there is growing evidence that the benefit of irradiation of regional undissected lymph nodes for selected patients with one to three positive axillary lymph nodes (pN1a) is as equal as has been demonstrated for those with four or more involved lymph nodes (pN2a) (Marks et al. 2008; Russel et al. 2009).

Radiation use was independently associated with improved survival for patients with Stage II breast cancer with one to three positive lymph nodes (Buchholz 2009, 2011; Darby 2009; Jagsi and Pierce 2009). Because multivariate analyses of retrospective data cannot account for all potential biases, these data require confirmation in randomized clinical trials (LoE Ib) (Buchholz 2008).

Patients with 1-3N+ and young age, Grade III, or ER-negative disease have high LRR risks approximating 15% to 20% despite BCS, whole-breast RT and systemic therapy. These patients may benefit with more comprehensive RT volume encompassing the regional nodes (Darby 2009; Jagsi and Pierce 2009; Truong et al. 2009).

In the pTNM classification system of UICC 2002, which has been refined in 2010, nodal status of breast cancer is based on the number of involved lymph nodes and does not account for the total number of lymph nodes removed. Numerous studies suggest that lymph nodal ratios (LNR; ie, ratio of positive over excised lymph nodes) may have greater prognostic value than absolute numbers of involved nodes. This has been supported by a systematic review and in multiple reports from both prospective and retrospectively collected data sets, respectively. The prognostic value of the LNR was compared with pN staging and its optimal cutoff points were determined by the International Nodal Ratio Working Group (Truong et al. 2008; Vinh-Hung et al. 2009; Woodward et al. 2006). In summary, LNR have been shown to be significant predictors of outcome, including locoregional recurrence and overall survival. LNR predicts survival after breast cancer more accurately than pN classification and should be considered as an alternative to pN staging. Consequently, this might be of influence for accurate indications for radiation therapy of regional lymphatics more precisely.

Extracapsular tumor spread (ECS) has been identified as a possible risk factor for breast cancer recurrence, but controversy exists regarding its role in decision making for regional radiotherapy. The International Breast Cancer Study Group has evaluated extracapsular tumor spread as a predictor of local, axillary, and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. In the International Breast Cancer Study Group Trial IV 1.475 eligible pre- and perimenopausal women with node-positive breast cancer were accrued. The authors concluded, that the results of this trial indicate that the decision for additional regional radiotherapy should not be based solely on the presence of ECS (Gruber et al. 2008).

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (9/11)

Further information and references:

Indikationsstellung zur Radiotherapie der regionalen Lymphabflussregionen

Neu 2013:

Metaanalysen:

Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer – meta-analysis of randomized trials. *Radiat Oncol* 2013; 8:267: additional regional lymph nodes irradiation of medial supraclavicular and internal mammary for patients with positive axillary sentinel nodes provide statistically significant benefits regarding disease-free survival, distant metastases-free survival and overall survival, respectively

Li Y, Moran MS, Huo Q, Yang Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. *PLoS One* 2013;8:e81765. doi: 10.1371/journal.pone.0081765.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. *Breast Cancer* 2014;21:1-9. doi: 10.1007/s12282-013-0497-8. Epub 2013 Oct 8.2013

Recommendations in updated guidelines:

Alberta Health Services (AHS), Canada, published March 1, 2013: Adjuvant Radiotherapy for Invasive Breast Cancer: “with RNI”

Belgian KCE-Guidelines, KCE Reports 143, updated July 8, 2013 (3rd edition): Wildiers H, Stordeur S, Vlayen J, et al. Breast cancer in women: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2013, 3rd edition. D/2013/10.273/38: “should be discussed on a case by case basis in the multidiscipline team meeting (expert opinion)”

Cardoso F, Loibl S, Paganì O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77: “Young patients should be informed the high local recurrence risk if radiation therapy is avoided....Internal mammary chain irradiation should be discussed on the basis of clinical, histopathological and radiological findings in the multidisciplinary team (LoE expert opinion)”

Sautter-Bihl ML, Sedlmayer F, Budach W, et al.; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines: radiotherapy of breast cancer III: - Radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014;190: in press

Scottish Intercollegiate Guidelines Network (SIGN), updated September 1, 2013: Treatment of primary breast cancer (SIGN CPG 134): strongly recommendation for participation in ongoing clinical trials (SUPREMO). – RT of supraclavicular fossa: “No RCTs were identified to guide the use of supraclavicular fossa radiotherapy after axillary clearance in patients with positive lymph node involvement....Participation in clinical trials should be encouraged”.

National Comprehensive Cancer Network (2013) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 3.2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; also in: Theriault RL, Carlson RW, Allred C, et al. Breast Cancer – Version 3.2013. *JNCCN* 2013;11:753-761: “1-3 positive lymph nodes: strongly consider radiation therapy to infraclavicular region and supraclavicular area (category 2B). strongly consider radiation therapy to internal mammary nodes (category 2B).” (Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate)

Further references:

Caretta-Weyer H, Greenberg CG, Wilke LG, et al. Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on Clinical Management of the Axilla in Older Breast Cancer Patients: A SEER-Medicare Analysis. *Ann Surg Oncol* 2013;20:4145-52

Chang JS, Park W, Kim YB, Lee IJ, Keum KC, Lee CG, Choi DH, Suh CO, Huh SJ. Long-term survival outcomes following internal mammary node irradiation in stage II-III breast cancer: results of a large retrospective study with 12-year follow-up. *Int J Radiat Oncol Biol Phys* 2013;86:867-72.

Courdi A, Chamorey E, Ferrero J-M, et al. Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. *Radiother Oncol* 2013;108:259-265.

Hennequin C, Bossard N, Servagi-Vernat S, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. *Int J Radiat Oncol Biol Phys* 2013;86:860-866.

Jagsi R, Pierce L. Radiation therapy to the internal mammary nodal region in breast cancer: the debate continues. *Int J Radiat Oncol Biol Phys* 2013;86:813-815

Karam I, Lesperance MF, Berrang T, et al. pN0(i+) Breast Cancer: Treatment Patterns, Locoregional Recurrence, and Survival Outcomes. *Int J Radiat Oncol Biol Phys* 2013;87:731-737.

Kim SI, Cho SH, Lee JS, Moon HG, Noh WC, Youn HJ, Ko BK, Park BW. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. *Br J Cancer* 2013;109:1165-71.

Liu D, Chen Y, Deng M, et al. Lymph node ratio and breast cancer prognosis: a meta-analysis. Breast Cancer 2014;21:1-9. doi: 10.1007/s12282-013-0497-8. Epub 2013 Oct 8.2013

Abstract

Due to the heterogeneity of lymph node examination and the conflicting results existing for the same classification of lymph node ratio (LNR), it is necessary to conduct a meta-analysis to evaluate the prognostic effects of different LNRs on breast cancer. PubMed, EMBASE, and ISI Web of Knowledge were searched to find all published cohort studies that evaluated the prognostic value of different LNRs on breast cancer. The outcomes were overall survival (OS), disease-free survival (DFS), breast cause-special survival (BCCS), mortality, locoregional recurrence (LRR), and distant metastasis. Data was analyzed using comprehensive meta-analysis software version 2.0, and 23 studies were included. The available evidence showed that LNR was a prognostic predictor for breast cancer, especially for clinically node-positive breast cancer, but the available evidence could not judge which cutoff point is the most reliable. Meanwhile, the cutoff values 0.2 and 0.65 could be suitable to predict breast cancer OS, DFS, BCCS, and mortality.

Offersen BV, Nielsen HM, Overgaard M, Overgaard J. Is regional nodes radiotherapy an alternative to surgery? Breast 2013;22 Suppl 2:S118-28. doi: 10.1016/j.breast.2013.07.023.

Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. Eur J Cancer 2013;49 (Suppl 3): S1 abstract BA2

Rutgers EJ, Donker M, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial (10981/22023. J Clin Oncol 2013;31,Abstract LBA1001.

Guidelines 2012 / recommendations 2012 for irradiation of the locoregional lymphatics

a) Mammacarcinoom. Landelijke richtlijn, Versie: 2.0. Datum Goedkeuring: 13-02-2012. Richtlijn Mammacarcinoom. Evidenced-based Guideline 13.02.2012: www.oncoline.nl/mammacarcinoom.

b) Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. 3. Auflage: Aktualisierung 2012. Zuckschwerdt Verlag, 2012 ISBN: 978-3-86371-073-6

c) Besnard S, Cutuli B, Fourquet A, et al. Radiothérapie du cancer du sein infiltrant: recommandations nationales françaises [Radiotherapy of invasive breast cancer: French national guidelines.] Cancer Radiother 2012;16:503-513 French.

Cutuli B. [Radiotherapy for breast cancer: Which strategy in 2012?]. Cancer Radiother 2012;16:493-502

e) Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012;13:e148-60

f) National Comprehensive Cancer Network (NCCN USA) Guidelines: NCCN-Practice Guidelines - Breast cancer Version: V.3.2012 (<http://www.nccn.org>)

Important prospective data recently suggested that internal mammary chain radiotherapy would not be necessary, even in cases of internal or central tumor locations, or in patients with positive axillary lymph nodes. Although these data warrant confirmation by two other prospective trials, there is evidence that the indications for internal mammary chain radiotherapy should be careful and that high quality techniques should be used for decreasing the dose delivered to the heart. This review of literature presents the state of art on the radiotherapy of internal mammary chain, with special focus on the indications, techniques, and potential toxicity.

Belkacémi Y, Fourquet A, Cutuli B, et al. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. *Crit Rev Oncol Hematol* 2011;79:91-102

Cardoso F, Stordeur S, Vlayen J, et al. Scientific support of the College of Oncology: update of the national guidelines on breast cancer. Good Clinical Practice (GCP). Brussels. Belgian Health Care Knowledge Centre (KCE). 2010. KCE Reports 143C. D/2010/10.273/77

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378(9804):1707-16.

National Comprehensive Cancer Network (NCCN USA) Guidelines: NCCN-Practice Guidelines - Breast cancer Version: V.2.2011 (<http://www.nccn.org>)

Further information:

The management of internal mammary nodes (IMN) in breast cancer is controversial. Surgical series from the 1950s showed that one third of breast cancer patients had IMN involvement, with a higher risk in patients with medial tumors and/or positive axillary nodes. IMN metastasis, a major independent prognostic factor in breast cancer patients, has similar prognostic importance as axillary nodal involvement.

After three randomized trials showed no survival benefit from extended mastectomy compared with radical or modified radical mastectomy, IMN dissection was largely abandoned. Recently, lymphoscintigraphy studies have renewed interest in IMN evaluation. Approximately one fifth of internal mammary sentinel nodes are pathologic, although most centers do not perform IMN biopsies or sampling of IM sentinel nodes (IMSN) because of concerns about morbidity and lack of established survival benefit.

It has been demonstrated, evaluation of IMISN improves nodal staging in breast cancer (Heuts et al. 2009). Patients with IM hotspots on lymphoscintigraphy have a substantial risk (22%) of metastatic involvement of the IM chain. In addition, true IM node-negative patients can be spared the morbidity associated with adjuvant radiotherapy.

Two large randomized trials (French Group-trial (n = 1.334 pts.; Romestaing et al. 2009), European Organization for Research and Treatment of Cancer [EORTC]-Trial 22922/10925 (n = 4.004 pts.)) are currently evaluating the possible benefit of irradiation of the internal mammary lymphatics. Thus, the role of irradiation of the internal mammary lymphatics will be revealed after 2010 by results of several prospective trials, for example the EORTC phase III randomized trial 22922/10925 or a trial of a French Group. Before mature results from current randomized trials assessing the benefit of IMN irradiation become available, lymphoscintigraphy may be used to help guide decisions regarding systemic and local-regional treatment (Heuts et al. 2009).

The updated recommendations of the NCCN 2010 state, that if internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes. CT treatment planning should be utilized in all cases, where radiation therapy is delivered to the internal mammary lymph node field (NCCN 2010).

However, even in patients with visualized primary IMN drainage, the potential benefit of treatment should be balanced against the risk of added morbidity (Romestaing et al. 2009; NCCN 2010).

Concomitant Use of Systemic Therapy with Radiotherapy (10/11)

Further information and references:

Kombination von systemischen antineoplastischen Therapien mit der Radiotherapie:

Sequenz RT und endokrine systemische Therapie

Karlsson P, Cole BF, Colleoni M, et al.; International Breast Cancer Study Group. Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy. *Int J Radiat Oncol Biol Phys* 2011;80:398-402.

RT concurrent to aromatase inhibitors

Belkacémi Y, Fourquet A, Cutuli B, et al. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. *Crit Rev Oncol Hematol* 2011;79:91-102

Valakh V, Trombetta MG, Werts ED, et al. Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. *Am J Clin Oncol* 2011;34:245-8

RT concurrent to tamoxifen

Munshi A, Gupta D. Concurrent versus sequential radiotherapy and tamoxifen in breast cancer - The CONSET trial is launched. *Acta Oncol* 2011;50:154-5.

Chargari C, Levy A, Védrine L, Magné N. Current trials of cytotoxic and targeted agents in breast cancer: the caveat of radiotherapy. *Ann Oncol* 2011;22:1243-1244.

Ishitobi M, Nakahara S, Komoike Y, et al. Risk of ipsilateral breast tumor recurrence in patients treated with tamoxifen or anastrozole following breast-conserving surgery with or without radiotherapy. *Anticancer Res* 2011;31:367-371.

2010-2012:

Azria D, Belkacemi Y, Romieu G, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. *Lancet Oncol* 2010;11:258-265.

Azria D, Betz M, Bourgier C, Sozzi WJ, Ozsahin M. Identifying patients at risk for late radiation-induced toxicity. Crit Rev Oncol Hematol 2012c;84 Suppl 1:e35-41

Balduzzi A, Leonardi MC, Cardillo A, et al. Timing of adjuvant systemic therapy and radiotherapy after breast-conserving surgery and mastectomy. Cancer Treat Rev 2010;36:443-450.

Belkacémi Y, Gligorov J, Chauvet MP, et al. [Radiotherapy and combined therapy in breast cancer: Standards and innovations in the adjuvant setting.] J Gynecol Obstet Biol Reprod (Paris) 2010;39(8 Suppl):F63-9

Belkacemi and J. Gligorov, Concurrent trastuzumab — internal mammary irradiation for HER2 positive breast cancer: “It hurts to be on the cutting edge”. Radiother Oncol 2010;94:119-20 (Letter to the editor).

Fernando IN, Bowden SJ, Buckley L, et al., on behalf of the SECRAB Steering Committee. SECRAB: The optimal SEquencing of adjuvant Chemotherapy (CT) and Radiotherapy (RT) in early Breast cancer (EBC), results of a UK multicentre prospective randomised trial. SABCS 2010; [S4-4], no full paper version available.

Recht A. Radiotherapy, antihormonal therapy, and personalised medicine. Lancet Oncol 2010;11:215-216.

Tsoutsou PG, Belkacemi Y, Gligorov J, et al.; on behalf of the Association of Radiotherapy and Oncology in the Mediterranean area (AROME). Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. Oncologist 2010;15:1169-78

Winzer KJ, Sauerbrei W, Braun M, et al.; German Breast Cancer Study Group (GBSG). Radiation therapy and tamoxifen after breast-conserving surgery: updated results of a 2 x 2 randomised clinical trial in patients with low risk of recurrence. Eur J Cancer 2010;46:95-101.

Sequenz RT und Trastuzumab:

Further information:

The human epidermal growth factor receptor-2 (HER2) is overexpressed and/or amplified in up to 25% of breast cancer patients, and this feature is associated with an aggressive phenotype, high recurrence rate and reduced survival. Trastuzumab combined with chemotherapy has been recently shown to improve outcome in HER2-positive breast cancer. However, many questions related to trastuzumab use in the adjuvant setting including concurrent radiotherapy still have to be answered.

Evaluation of possible toxic effects of concurrent radiation therapy and administration of trastuzumab in the adjuvant setting is under investigation. So far, acute toxicity analyses and data from clinical observation studies of breast cancer patients treated with trastuzumab and concurrent radiotherapy with irradiation of internal mammary chain with, in most cases, anthracycline-based chemotherapy revealed no significant increase in the rate of abnormal LVEF (Halyard et al. 2009). There was no excess acute cardiotoxicity observed with the combination of left-sided IMC

irradiation and concurrent trastuzumab (Halyard et al. 2009; Shaffer et al. 2009). Even more, skin toxicity was acceptable in routine (Kirova et al. 2009).

More patients and a longer follow-up are needed to ascertain that this regimen with concurrent radiotherapy and trastuzumab is safe and feasible without compromising therapeutic benefit. However, cardiac volume sparing and patient selections for IMC irradiation are highly recommended. Longer follow-up is warranted to evaluate late toxic effects.

References:

Belkacémi Y, Gligorov J, Ozsahin M, et al. Concurrent trastuzumab with adjuvant radiotherapy in HER2-positive breast cancer patients: acute toxicity analyses from the French multicentric study. *Ann Oncol* 2008;19:1110-6

Bollet MA, Kirova YM, Granger B, et al. Preliminary result of a mono-institutional, prospective study of skin and cardiac toxicities in breast cancer patients treated by concurrent adjuvant trastuzumab and radiotherapy involving in most cases the internal mammary chain. *SABCS 2008*, abstract # 5132

Chung C, Stuart D, Keves M. Radiation recall reaction induced by adjuvant trastuzumab (Herceptin). *Case Report Med* 2009;2009:307894. Epub 2009 Sep 8

Dinh P, de Azambuja E, Cardoso F, Piccart-Gebhart MJ. Facts and controversies in the use of trastuzumab in the adjuvant setting. *Nat Clin Pract Oncol* 2008;5:645-54

Halyard MY, Pisansky TM, Dueck AC, et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. *J Clin Oncol* 2009;27:2638-44:

1.503 irradiated patients with early-stage resected human epidermal growth factor receptor 2 (HER-2)-positive breast cancer were enrolled in the NCCTG Phase III Trial N9831, who were randomly assigned to doxorubicin and cyclophosphamide, followed by weekly paclitaxel, trastuzumab and sequential radiotherapy. An analysis was performed, to assess whether trastuzumab with radiotherapy increases adverse events after breast-conserving surgery or mastectomy. In this trial the radiotherapy was performed either as postlumpectomy breast or (optional) postmastectomy chest wall irradiation. However, concurrent radiotherapy of internal mammary nodes was prohibited. - At a median follow-up of 3.7 years (range, 0 to 6.5 years), radiotherapy with trastuzumab did not increase relative frequency of cardiac events regardless of treatment side. Thus, concurrent adjuvant radiotherapy and trastuzumab for early-stage breast cancer was not associated with increased acute adverse events. Further follow-up is required to assess late adverse event (Halyard et al. 2009).

Halyard M, Pisansky TM, Pierce LJ, et al. Changes in left ventricular function after radiation therapy and Trastuzumab: Analysis of North Central Cancer Treatment Group Phase III Trial N9831. *IORBP 2009*;75, Supplement. S50: abstract #106

Kirova YM, Caussa L, Granger B, et al. [Monocentric evaluation of the skin and cardiac toxicities of the concomitant administration of trastuzumab and radiotherapy]. *Cancer Radiother* 2009;13:276-80.

Shaffer R, Tyldesley S, Rolles M, et al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: A retrospective single-institution study. *Radiother Oncol* 2009;90:122-126

Conclusions: There was no excess acute cardiotoxicity observed with the combination of left-sided IMC irradiation and concurrent trastuzumab.

In the Scottish and Institut Curie experiences, the concomitant administration of trastuzumab with RT of the IMC does not seem to be deleterious to the heart in the short- or middle-term (Kirova et al. 2009; Shaffer et al. 2009). However, regarding the short term of follow-up in these published studies and the uncertainties concerning the use of LVEF to predict late cardiac toxicity, it should be recommended to strongly limit the dose to the heart structures when RT of the IMC is delivered

Aromatase Inhibitors und simultane RT

Azria D, Belkacemi Y, Romieu G, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. *Lancet Oncol* 2010;11:258-65.

BACKGROUND: Letrozole radiosensitises breast cancer cells in vitro. In clinical settings, no data exist for the combination of letrozole and radiotherapy. We assessed concurrent and sequential radiotherapy and letrozole in the adjuvant setting.

METHODS: This phase 2 randomised trial was undertaken in two centres in France and one in Switzerland between Jan 12, 2005, and Feb 21, 2007. 150 postmenopausal women with early-stage breast cancer were randomly assigned after conserving surgery to either concurrent radiotherapy and letrozole (n=75) or sequential radiotherapy and letrozole (n=75). Randomisation was open label with a minimisation technique, stratified by investigational centres, chemotherapy (yes vs no), radiation boost (yes vs no), and value of radiation-induced lymphocyte apoptosis (< or = 16% vs >16%). Whole breast was irradiated to a total dose of 50 Gy in 25 fractions over 5 weeks. In the case of supraclavicular and internal mammary node irradiation, the dose was 44-50 Gy. Letrozole was administered orally once daily at a dose of 2.5 mg for 5 years (beginning 3 weeks pre-radiotherapy in the concomitant group, and 3 weeks post-radiotherapy in the sequential group). The primary endpoint was the occurrence of acute (during and within 6 weeks of radiotherapy) and late (within 2 years) radiation-induced grade 2 or worse toxic effects of the skin. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00208273.

FINDINGS: All patients were analysed apart from one in the concurrent group who withdrew consent before any treatment. During radiotherapy and within the first 12 weeks after radiotherapy, 31 patients in the concurrent group and 31 in the sequential group had any grade 2 or worse skin-related toxicity. The most common skin-related adverse event was dermatitis: four patients in the concurrent group and six in the sequential group had grade 3 acute skin dermatitis during radiotherapy. At a median follow-up of 26 months (range 3-40), two patients in each group had grade 2 or worse late effects (both radiation-induced subcutaneous fibrosis).

INTERPRETATION: Letrozole can be safely delivered shortly after surgery and concomitantly with radiotherapy. Long-term follow-up is needed to investigate cardiac side-effects and cancer-specific outcomes.

Further references:

Ishitobi M, Komoike Y, Motomura K, et al. Retrospective analysis of concurrent vs. sequential administration of radiotherapy and hormone therapy using aromatase inhibitor for hormone receptor-positive postmenopausal breast cancer. *Anticancer Res* 2009;29:4791-4.

Kesisis G, Makris A, Miles D. Update on the use of aromatase inhibitors in early-stage breast cancer. *Breast Cancer Res* 2009;11:211

Radiotherapy in the Elderly Patient (11/11)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Therapy Side Effects

Therapy Side Effects

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Toxicity Assessment

Acute Toxicity According to WHO¹ or NCI-CTC²

Grade

- 0 none**
- 1 mild**
- 2 moderate**
- 3 severe**
- 4 life threatening**

Information required

- organs involved**
- type of toxicity**
- time interval after treatment**
- effect on general health status**
- treatment required**
- recovery achieved**

Long-Term Toxicity No general assessment scale

¹ WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)

² NCI, NHI, Bethesda, USA, Common Toxicity Criteria, CTCAE v4.0 , (2010) <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

Cytotoxic Anti-Cancer Drugs – Acute Toxicity I

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| | Haematol. Toxicity | Nausea/ Vomit. | Alopecia | Mucositis/ Stomatitis | Cardiac Toxicity | Renal Toxicity | Hepatic Toxicity |
|-------------------------------------|-----------------------|-------------------|----------|--------------------------|---------------------|-------------------|---------------------|
| Cyclophosphamide | ++ | ++ | + | + | + | ++ | |
| Methotrexate | ++ | + | + | ++ | + | ++ | + |
| 5-Fluorouracil | ++ | ++ | | ++ | + | | |
| Carboplatin | ++ | ++ | + | | | ++ | |
| Cisplatin | + | +++ | | | | +++ | |
| Capecitabine | + | + | | + | | | |
| Gemcitabine | ++ | + | | + | | | + |
| Epi-/Doxorubicin | ++ | ++ | +++ | ++ | + | | |
| Pegliposomal Doxorubicin | + | + | + | ++ | (+) | | |
| Liposomal Doxorubicin | + | + | + | ++ | (+) | | |
| Mitoxantrone | ++ | ++ | + | + | + | | |
| Paclitaxel | ++ | + | +++ | + | | | + |
| nab-Paclitaxel | + | + | +++ | | | | + |
| Docetaxel | ++ | + | +++ | ++ | | | |
| Vinorelbine | ++ | | (+) | + | | | |
| Eribulin | ++ | + | + | | | | |

Cytotoxic Anti-Cancer Drugs – Acute Toxicity II

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| | Allergic Reaction | Bladder Toxicity | Neuro- pathy | Skin Toxicity | Diarrhea | Hand- Foot-S. | Other |
|---------------------------|----------------------|---------------------|-----------------|------------------|----------|------------------|-------------------------------------|
| Cyclophosphamide | + | + | + | + | | | |
| Methotrexate | + | | + | ++ | | | |
| 5-Fluorouracil | | | | + | + | + | |
| Carboplatin | | | | | | | |
| Cisplatin | | | +++ | | | | |
| Capecitabine | | | | | ++ | ++ | |
| Gemcitabine | | | | | | | Flue-like Synd., Oedema |
| Epi-/Doxorubicin | + | | | | | | Paravasates, Dextraxozane |
| Liposomal Doxo. | + | | | + | | | |
| Pegliposomal Doxo. | + | | | +++ | | | |
| Mitoxantrone | | | | ++ | | | |
| Paclitaxel | +++ | | ++ | | + | | Myalgia |
| nab-Paclitaxel | + | | ++ | | + | | Myalgia |
| Docetaxel | ++ | | + | ++ | + | | Myalgia, Fluid retention, nails! |
| Vinorelbine | | | ++ | | | | Thrombophlebitis |
| Eribulin | | | ++ | | | | Obstipation |

Long-Term Toxicity

Cardiotoxicity

Oxford / AGO
LoE / GR

- **Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)** **2b B**
- **Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity** **1b B**
- **Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:** **2b B**
 - **Elderly patients**
 - **Obesity**
 - **Hypertension**
 - **Hypercholesterolemia**
 - **Pre-existing cardiac diseases (incl. borderline LVEF)**
 - **Diabetes mellitus**
- **Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)** **3b C +**

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Feasibility of Treatment Combinations Considering Toxicities

**Oxford / AGO
LoE / GR**

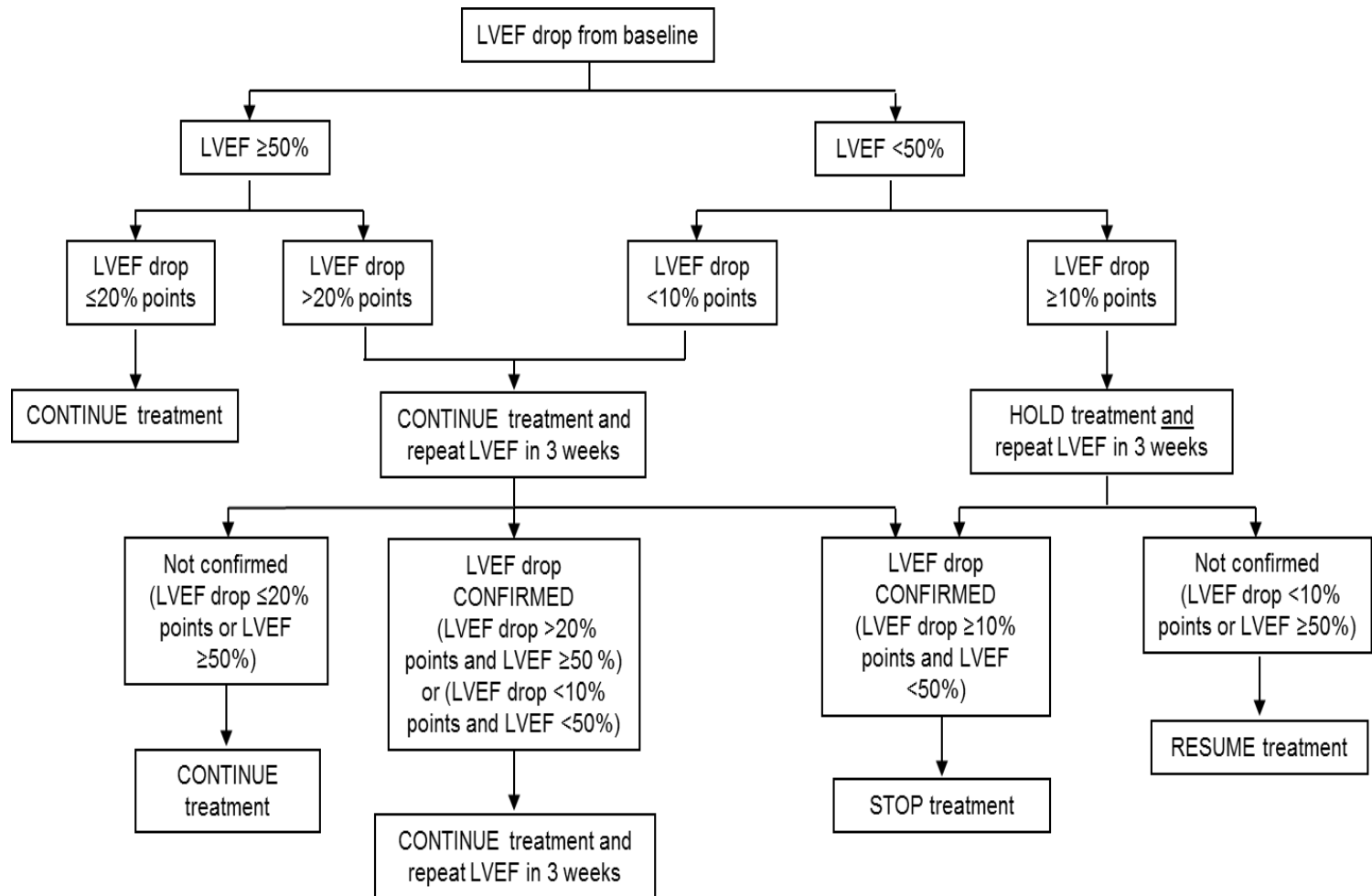
Regarding cardiac toxicity

| | | | |
|--|-----------|----------|------------|
| ➤ Trastuzumab simultaneous to radiotherapy | 2b | B | + |
| ➤ Trastuzumab simultaneous to epirubicin | 2b | B | +/- |
| ➤ Trastuzumab simultaneous to doxorubicin | 2b | B | - |
| ➤ Anthracycline simultaneous to radiotherapy | 2c | C | - |

Regarding lung and breast fibrosis

| | | | |
|---|-----------|----------|------------|
| ➤ Tamoxifen simultaneous to radiotherapy | 3 | C | +/- |
| ➤ Chemotherapy simultaneous to radiotherapy | 1b | B | - |

Side Effects of Trastuzumab/Pertuzumab Algorithm in Case of Cardiac Toxicity



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Secondary Malignancies I

Oxford LoE

- **With regard to solid tumours, chemotherapy induced secondary malignancies are rare events**
- **Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0,2–0,4 % within 10 - 15 years**
- **Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0,2–1,7 % within 8 to 10 years**
- **Radiotherapy increases the risk of leukaemia by 0,2–0,4% in patients treated with anthracycline-containing chemotherapy**
- **Tamoxifen approximately doubles the risk for developing endometrial cancer**

2a

2a

2a

2b

2b

Secondary Malignancies II (after Radiotherapy)

Oxford
LoE

- **The risk of developing secondary cancers is low if modern radiation techniques are applied and should not deter the use of radiotherapy when indicated**
- **Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma appearing 5–10 years after treatment**
 - **Enhanced risk especially among ever smokers**

2b

1a

2b

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Chemotherapy Related Amenorrhea (CRA)

Oxford
LoE

- **CRA may be permanent or temporary**
- **Depends on CTX regimen used**
- **CRA is an (imperfect) surrogate for menopause and fertility**
- **Adjuvant endocrine therapy induces reversible amenorrhea, but delays conception to a less fertile period**
- **Risk of CRA increases with age / treatment duration** **2b**
- **Ovarian reserve of women who remain premenopausal after CTX is reduced** **2b**
- **CRA is associated with improved outcome (DFS/OS)** **1b**

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)

(Therapy Related) Fatigue

**Oxford / AGO
LoE / GR**

- **Fatigue frequently present in breast cancer patients (30–60%)** **2a B**
- **Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue** **1a A ++**
- **Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue** **1a A ++**
- **Physical exercise with ambiguous effects regarding fatigue** **1b D +**
- **Methylphenidate might improve fatigue** **1a D +**

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(Therapy Associated) Sleeping disturbance

Oxford / AGO
LoE / GR

- **Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)**

2a B

- **Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life**

1b A ++

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(Therapy Associated) Depression

Oxford / AGO
LoE / GR

- **Depression is an often reported adverse event in breast cancer patients (20–30%)**
- **Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients**
- **Antidepressants have shown to improve depression in breast cancer patients**
- **Regular exercise participation can prevent depression among breast cancer survivors**

2a B

1b A

1b A

2b B +

(Therapy Associated) Cognitive Impairment

Oxford / AGO
LoE / GR

- **Therapy-related cognitive deficits
(chemobrain frequently described (16–75%))** **2a B**
- **Cognitive-behavioral therapy is beneficial for
cognitive function** **2b B**
- **Methylphenidate might improve cognitive
function in patients with cancer** **3a C**

Further
Information

References

Side-effects and Toxicity of Endocrine Agents

| | Visual Disturbances | Osteoporosis | Cerebro-Vascular Events * | Fracture | Cardiac risk | Cognitive functions |
|--------------------|---------------------|--------------|---------------------------|----------|--------------|---------------------|
| SERMs | (+) | | + | | | + |
| AI 3rd Gen* | | + | | + | + | (+) |
| SERD | | + | | + | | |
| GnRHa | | + | | + | | |

| | Arthralgia Myalgia | Flush | Dysfunctional Bleeding* | Endometrial Changes | Deep Venous Thrombosis | Lipid Profile Impaired |
|------------------|--------------------|------------|-------------------------|---------------------|------------------------|------------------------|
| SERMs | (+) | + | + | + | (+) | |
| | (+) | + | + | + | | |
| Als | + | (+) | | | | (+) |
| SERD | | | | | | |
| Goserelin | (+) | + | | | | |

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Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

**Oxford
LoE**

- **Renal function deterioration due to IV-amino-BP**
- **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%)**
- **Acute phase reaction (IV Amino-BPs, DB) 10–30%**
- **Gastrointestinal side effects (oral BPs) 2–10%**

1b

1b

1b

2b

**In adjuvant bisphosphonate therapy,
major side effects were observed rarely (except APR)**

Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4

GR: C

AGO: +

- During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (**LoE 2b**)
- Optimize dental status before start of bisphosphonate treatment, if feasible (**LoE 2b**)
- Inform patients about ONJ risk and educate about early symptom reporting
- In case of high risk for ONJ, use oral bisphosphonate

**In adjuvant bisphosphonate therapy,
ONJ was rare**

Frequent Side Effects of Bone Modifying Agents (BMA)

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| Drug | Acute Phase React. | Renal Tox. | Upper GI-SE | Diar- rhea | ONJ | |
|---------------------------|--------------------------|---------------|----------------|---------------|-----|-------------------|
| Clodronate 1500 i.v. | 0 | + | 0 | 0 | 0 | |
| Clodronate 1600 p.o. | 0 | 0 | + | + | 0 | Non-A |
| Ibandronate 50 mg p.o. | 0 | 0 | + | 0 | 0 | Amino |
| Ibandronate 6 mg i.v. | + | 0 | 0 | 0 | + | |
| Zoledronate 4 mg i.v. | + | + | 0 | 0 | + | |
| Pamidronate 90 mg i.v. | + | + | 0 | 0 | + | |
| Zoledronate 4 mg i.v. q6m | 0 | 0 | 0 | 0 | 0 | |
| Denusomab 120 mg sc q4w | 0 | 0 | 0 | + | + | Hypo- calcemia |

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Key-Toxicities – Small Molecules / Antibodies

Trastuzumab

- Cardiotoxicity in the adjuvant setting (0,8–4,0%)
- Troponin I might identify patients who are at risk for cardiotoxicity

Oxford / AGO
LoE / GR

1b A

2b B

Pertuzumab

- Skin rash, diarrhea, mucositis

2b B

T-DM1

- Thrombocytopenia, hepatotoxicity
pyrexia, headache, pneumonitis

2b B

Lapatinib

- Diarrhea, skin rash, fatigue

1b A

Bevacizumab

- Hypertonus, proteinuria, bleeding, left ventricular dysfunction,

1a A

Everolimus

- Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, Thrombocytopenia

2b B

Therapy Side Effects (2/20)

Further information:

Screened data bases: Pubmed 2007 - 2013, ASCO 2010 – 2013, SABCS 2010 – 2013, Cochrane data base (2013)

Screened guidelines:

NCI (National Cancer Institute , 2012): <http://www.cancer.gov>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2012) <http://www.asco.org>

CMA (Canadian Medical Association , 2012): <http://www.cmaj.ca>

NCCN (National Comprehensive Cancer Network , 2012): <http://www.nccn.org>

No references

Toxicity Assessment (3/20)

Further information:

Acute toxicity and in most cases 100 day mortality rates are well documented in the majority of phase III trials. Toxicities are graded according to WHO or NCI standards. This implies that toxicities concerning liver, kidney heart or skin are well documented and graded. Other toxicities like fatigue, depression, menopausal symptoms or impairment of cognitive function are systematically underreported by these tools. Most trials end five or ten years after the last patient in, such that late and very late effects are rarely documented.

Acute Toxicity according to WHO1 or NCI-CTC2:

References:

1. WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010); <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (4/20)

No further information

References:

Shapiro CL, Recht A: Side effects of adjuvant treatment of breast cancer. N Engl J Med 344:1997-2008, 2001

Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.

Petrelli F et al: Mortality, leukemic risk, and cardiovascular toxicity of adjuvant anthracycline and taxane chemotherapy in breast cancer: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):335-46

Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012 Oct 10;30(29):3578-87

Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23

Kaufmann PA, Awada A, Twelves C et al. Phase 3 open label randomized multicenter study Eribulin Mesylate versus Capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclins and taxanes SABCS 2012, abstract S6-6

Cytotoxic Anti-Cancer Drugs – Acute Toxicity II (5/20)

No further information

References:
see slide 4

Long-Term Toxicity Cardiotoxicity I (6/20)

Further information:

Anthracycline (A) based standard chemotherapy regimens as used in the adjuvant therapy of breast cancer are associated with a relatively low acute toxicity and treatment related mortality rates < 1 %. In terms of long- term toxicity cardiotoxicity and secondary acute leukemia/MDS are clinically relevant.

Cardiotoxicity:

Early cardiotoxicity of anthracyclines has been well established in clinical trials. Limited data are available on long-term cardiac safety of A based regimens. As patients with breast cancer are getting older and as survival rates improve long term cardiotoxicity is of growing interest.

AC: Among patients treated with four cycles of AC on NSABP B31 17 % of patients developed asymptomatic cardiac disease defined as the decline in left ventricular ejection fraction of more than 10 % to an ejection fraction of less than 55 %. Similar data were presented recently by Perez et al. in N9831 trial. In 2992 patients completed AC 5% had LVEF decrease disallowing trastuzumab (decrease below normal: 2.4%, decrease > 15%: 2.6%).

FAC: The Southwest Oncology Group evaluated long term cardiotoxicity from patients randomized to protocol S8897. In this trial patients were randomized to CAF or to CMF. A was given on day 1 and 8. 180 patients from an potential sample of 1176 patients entered. There was no significant difference in the proportion of women with an LVEF less than 50 % at 5 to 8 years (CAF vs. CMF: 8% vs. 5%, p=0.68) or at 10 to 13 years (CAF vs. CMF: 3% vs. 0%, p=0.16). However in an exploratory analysis the mean LVEF in the doxorubicin group was statistically significantly lower in the 5 to 8 year sample (p=0.01), but not in the 10 to 13 year sample.

French FEC: The FASG reports ten year follow –up data in patients receiving either FE50C or FE100C from FASG 05. Delayed (> 1 month after the end of chemotherapy) symptomatic cardiotoxicity was reported in 1.5 % of patients from the FE50C arm and in 1.1 % of patients from the FE100C arm. In summary early and delayed cardiotoxicity was reported in 4.3 % and in 4.8 % of patients.

The second analysis from the FASG trials compared E+ and E- (antihormonotherapy or nil) regimens in 3577 breast cancer patients. E+ therapy was associated with 1.36% decrease in LVEf after 7 years vs. only 0.21% in controls (p=0,004). In these analysis age > 65 years old and body mass index > 27 were significant predictors of cardiac toxicity.

A containing regimens outside clinical trials in the elderly

There are 2 important studies from the SEER database in older women. The first one by Doyler et al. analyzed data from 31478 patients, 5575 of them received A-based chemotherapy (18%). This study highlights bias of all studies, investigating cardiac affects of A-chemotherapy, because these patients are per se younger, with less comorbidities and a higher risk of recurrence. The hazard ratios for cardiomyopathy, cardiac failure, and heart disease for patients > 65 years treated with doxorubicin compared with patients who received no chemotherapy were 2.48 (95% CI, 2.10 to 2.93), 1.38 (95% CI, 1.25 to 1.52), and 1.35 (95% CI, 1.26 to 1.44), respectively. The relative risk remained elevated 5 years after diagnosis. Preexisting heart disease was beside of afro-american race the most important risk factor for cardiac failure after A-exposure.

Pinder et al reported data from a total of 43.338 women from the SEER'S database. Similarly as in the previous study anthracycline-treated women were younger, with less comorbidity and had more advanced diseases than women who received non anthracycline based regimens. The adjusted hazard ratio was 1.26 for women aged 66 to 70 treated with a compared other chemotherapy. In this age group at five years of follow-up the observed absolute differences were of 1 % and 4.6 % respectively in rates of chronic heart failure between anthracycline based chemotherapy and other adjuvant chemotherapy or no chemotherapy. After ten years the increased risk of chronic heart failure was amplified rather than attenuated, with absolute differences of 5.9 % and 9.7 % when comparing anthracycline treated patients to the other or no adjuvant chemotherapy groups. For women aged 71 to 80 adjuvant chemotherapy was not associated with chronic heart failure.

Taxanes and cardiac safety

Data on cardiac safety in anthracycline-taxane sequential trials are in favour of taxane-based combinations, in which lower doses of anthracyclines are used. E.g. the PACS 01 trial reported significantly lower incidence of cardiac toxicity in the 3xFEC-3xDoc arm than in the 6xFEC arm (0.4% vs. 1.3%, $p=0.027$). These data have been confirmed in the Cochrane analysis, where trials in which total doses of anthracycline was reduced by substitution of taxane, had subsequently less cardiac events, than standard A-based regimens (OR=0.37 (95%CI: 0.14-0.95)). There are only limited data on cardiac safety of A-free regimens in adjuvant setting in breast cancer. Jones et al. reported 5 cardiac events in 510 patients treated by 4 cycles of AC and only 1 in 506 patients in the 4xTC arm in the US Oncology study.

In the BCIRG 006 study there were also significantly less patients with >10% decrease of LVEF value in the Taxotere/Carboplatin/Herceptin (TCH) arm than in AC-TH arm (8% vs. 17,3%), although the negative synergistic cardiac effect of Herceptin should be considered separately of anthracycline cardiac side effects.

Trastuzumab and cardiac safety

Most studies have excluded elderly patients (> 60 or 65 years) or patients with other risk factors (cardiovascular diseases, obesity, hypertension) from studies including trastuzumab. In clinical practice, 32% of HER2+ EBC patients treated with trastuzumab are 'over-60'. These patients have an increased cardiovascular risk profile and develop trastuzumab related cardiotoxicity commonly. Also with regard to other risk factors there is an increased risk of trastuzumab related cardiotoxicity during treatment, which is reversible after cessation of trastuzumab.

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Feasibility of Treatment Combinations Considering Toxicities (7/20)

Further information:

The frequency of adverse events for patients with HER-2 positive early breast cancer was examined in a randomized study with a median follow-up time of 3.7 years. 1503 patients were irradiated. Radiotherapy (RT) was administered either without or with concurrent trastuzumab (H). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of cardiac events (CEs) regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% v 5.9% with or without RT, respectively. Thus, concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (Halyard al, 2009). Reported data regarding the influence of tamoxifen given simultaneously to radiotherapy are diverging. Simultaneously given tamoxifen to radiotherapy might increase the risk of Grade 1 lung fibrosis ($p = 0.01$) and might increase the risk of late lung sequelae ($OR = 2.442$, 95% CI 1.120-5.326, $p = 0.025$). However other reports did not confirm such an connection. Therefore the results of the ongoing CONSeT-trials has to be awaited.

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Side Effects of Trastuzumab and Pertuzumab: Algorithm in Case of Cardiac Toxicity (8/20)

Further information:

Cardiotoxicity has been reported to occur with trastuzumab when administered alone and in combination with antineoplastic agents, particularly anthracyclines. The risk of cardiotoxicity with trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with an anthracycline and cyclophosphamide. However, severe and life-threatening damages are rare and the majority of reported cardiac effects are mild to moderate, nonspecific, and medically manageable. Signs and symptoms are similar to those observed in patients who develop anthracycline-induced cardiomyopathy and include tachycardia, palpitations, and exertional dyspnea, which may ultimately progress to congestive heart failure (Keefe, 2002). Trastuzumab-associated toxicity usually responds to standard treatment or the discontinuation of trastuzumab, and there is no evidence that the toxicity is dose related. Left ventricular ejection fraction (LVEF) should be measured at baseline and at regular intervals. An algorithm based on LVEF changes is presented to aid in the question whether continuation of trastuzumab is safe and feasible or whether discontinuation is warranted.

There are also data for trastuzumab and pertuzumab from phase 2 trials and randomized phase 3 trials, in neither trial cardiotoxicity was increased through the addition of pertuzumab to trastuzumab both in the absence or presence of taxane containing chemotherapy. In the Cleopatra trial 808 pts with metastatic breast cancer were randomized to docetaxel and trastuzumab and placebo or to docetaxel and trastuzumab and pertuzumab. LVEF dysfunction (any grade) was more frequently seen in the placebo group than in the pertuzumab group (8,3% vs 4,4%). LVEF dysfunction of grade 3 or higher was reported in 2,8% and 1,2% of the patients in the placebo and pertuzumab arms respectively.

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Secondary Malignancies I (9/20)

Further information:

Approximately one in every 20 breast cancer patients developed a second non-breast primary tumour within 10 years following a breast cancer diagnosis (10 years cumulative incidence rate 5.4%; 95%CI 5.1 to 5.7). Compared with the general female dutch population, these breast cancer patients had a 22% increased relative risk in second non-breast primary cancers and an absolute excess risk of 13 cases per 10.000 women-years (13,6 (95%CI 9.7 to 17.6). The occurrence of a second non-breast cancer was associated with a decrease in overall survival (HR 3.98, 95%CI 3.77 to 4.20).¹

Standard incidence ratios were elevated for cancers of esophagus, stomach, colon, rectum, lung, uterus, ovary, kidney, bladder, soft tissue sarcomas, melanoma, non Hodgkin's lymphoma, acute myeloid leukemia.¹⁻³

Patients younger than 50 years, radiotherapy was associated with increased lung cancer risk (HR 2.31; 95%CI 1.15 to 4.60) and chemotherapy with decreased risk for all secondary non-breast cancers.^{1,2}

Patients 50 years and older, radiotherapy was associated with increased risk of soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04), chemotherapy with increased risk of melanoma, uterine cancer, acute myeloid leukemia and hormonal therapy with uterine cancer (HR 1.78, 95%CI 1.40 to 2.27).^{1,2}

Risk of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

Women with a prior breast cancer were ~2.6 times more likely to develop AML than the total female Australian population, with highest age-specific relative risk for AML in the 30- to 49-age group.¹

Mitoxantrone-based chemotherapy was associated with a higher leukemic risk than with anthracyclines (RR 16.8, 95%CI 7.1 to 34.2 than RR 2.7, 95%CI 1.7 to 4.5). Epirubicin and doxorubicin had a similar risk.²

For women > 65 years receiving polychemotherapy (CAF, ACP) the risk to develop grade 4 hematologic toxicity, to have discontinued treatment for toxicity or to die of acute myeloid leukemia/MDS was significantly elevated.³

Granulocyte colony-stimulating factor (G-CSF) increased the risk of developing AML/MDS.¹⁻⁵

Details to chemotherapy regimes:

French FEC

The French Adjuvant Study Group reviewed their 16-year experience with their FEC regimen of 5-Fluorouracil, epirubicin (50, 75, 100 mg/m²) and cyclophosphamide i.v. q3w. Cumulative epirubicin doses mostly were below 600 mg/m². As for leukemia, data of 3653 women are available, which were followed for a median of 104 months. About two-third of the patient population received epirubicin-based adjuvant chemotherapy while slightly lower than one-third received CMF-like regimens. The incidence of secondary leukemia was very low: 0.3 % for those patients treated with adjuvant epirubicin and <0.1 % for those treated with other adjuvant therapies (CMF-like, antihormonal therapy).

Canadian FEC

The National Cancer Institute of Canada Clinical Trials Group analysed the risk of secondary acute leukemia (sAL) following adjuvant therapy with regimens containing epirubicin. The analysis were performed to assess the conditional probability of sAL in 1545 women having received adjuvant (n = 1477) or neoadjuvant (n = 68) chemotherapy in four National Cancer Institute of Canada Clinical Trials Group trials from 1990 to 1999. The leukemia risks associated with epirubicin-containing regimens (CEF or EC) and other regimens as doxorubicin and cyclophosphamide (AC or CMF) were registered. A total of 10 cases of sAL were observed (eight acute myelogenous leukemia, two acute lymphoblastic leukemia): Seven among women treated with CEF, two who had received AC, and one following CMF. Using competing risk statistics, the conditional probability of sAL was 1.7 % (95 % confidence interval [CI], 0.5 to 3.6) among 539 women treated with CEF chemotherapy at a follow-up of 8 years, 0.4 % (95 % CI, 0 % to 1.3 %) among the 678 who received CMF, and 1.3 % (95 % CI, 0 % to 4.7 %) among the 231 treated with AC. Of note, Canadian CEF comprises epirubicin doses of 120 mg/m². The conditional probability for breast cancer death at 8 years for the whole group treated with epirubicin-containing regimens in all four trials was approximately 34.9%. The group concluded that CEF chemotherapy for breast cancer carries a small increased risk of sAL compared with CMF which has to be taken into account when discussing treatment options with patients who are at a lower risk of breast cancer death, e. g. node negative patients. The rates of acute leukemia had not changed since the original report when updated 10-years results have been reported in 2005.

US – AC

Purpose: We reviewed data from all adjuvant NSABP breast cancer trials that tested regimens containing both doxorubicin (A) and cyclophosphamide (C) to characterize the incidence of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Materials and Methods: Six complete NSABP trials have investigated AC regimens (B-15, B-16, B-18, B-22, B-23, and B-25). Six distinct AC regimens have been tested and are distinguished by differences in cyclophosphamide intensity, cumulative dose and by the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. In all regimens, A was given at 60 mg/m² q 21 days x 4. C was given as follows: 600 mg/m² q 21 days x 4 ("standard AC"); 1200 mg/m² q 21 days x 2; 1200 mg/m² q 21 days x 4; 2400 mg/m² q 21 days x 2; and 2400 mg/m² q 21 days x 4. Occurrence of AML/MDS was summarized by incidence per 1,000 patient-years at risk and by cumulative incidence. Rates were compared across regimens, by age, and by treatment with or without breast radiotherapy.

Results: The incidence of AML/MDS was sharply elevated in the more intense regimens. In patients receiving two or four cycles of C at 2400 mg/m² with granulocyte colony-stimulating factor (G-CSF) support, cumulative incidence of AML/MDS at 5 years was 1.01 % (95 % confidence interval [CI], 0.63 % to 1.62 %), compared with 0.21 % (95 % CI, 0.11 % to 0.41 %) for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR = 2.38, *P* = .006), and the data indicated that G-CSF may also be independently correlated with increased risk.

AML/MDS in older patients

In summary Conclusion for FEC and AC secondary AML/MDS rates correlate with regimens employing intensified doses of cyclophosphamide requiring G-CSF support and to a smaller extent which were characterized by increased rates of subsequent AML/MDS, although the incidence of AML/MDS was small relative to that of breast cancer relapse. Breast radiotherapy appeared to be associated with an increased risk of AML/MDS, but data are inconsistent (see slide 10/20).

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Secondary Malignancies II (10/20)

Further information:

Radiotherapy increased the risk of sarcoma and lung cancer.

Results of a Dutch population-based study, patients younger than 50 years, radiotherapy was associated with an increased lung cancer risk (HR 2.31, 95%CI 1.15 to 4.60) and patients older than 50 years were more likely to develop soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04).¹

According to the cohort data of the SEER registries 1973 to 2000 risk for second cancers was dose dependend.

Radiotherapy treatment assuming standard protocol with 50Gy tumour dose and beam energy 6 MV photons. The RR were 1.45 (95%CI 1.33 to 1.58) for high dose second cancer sites (1 +Gy, lung, oesophagus, pleuro, bone and soft tissue sarcoma) with no evidence of elevated risk for sites receiving medium (05.-0,9 Gy) or low doses (< 0,5 Gy). Overall risks were generally lower for patients treated in recent years (1993 +). But the pattern of risks observed were consistend with the general literature on radiation carcinogenesis, risks were higher for sites that should have received higher doses and also higher for young age at exposure.⁶⁻⁸

The risk of lung cancer was elevated for ever-smokers who receive PMRT (HR18.9, 95%CI 7.9-45.4) according the results of the nested breast cancer cohort study population of the Connecticut Tumor Registry.⁵

Data are inconsistent for an elevated risk of AML/MDS after radiation exposure.⁶⁻⁸

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Chemotherapy Related Amenorrhea (CRA) (11/20)

Further information:

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)

Preservation of ovarian function is an important issue in the population of breast cancer patients especially in the patient younger than 40. Up to now neither data for ovarian protection with e.g. GnRH analogues nor cryopreservation of ovarian tissue are convincing. The treatment compromising most often fertility is chemotherapy.¹ After modern taxan-anthracyclin containing chemotherapy the risk of CRA is markedly lower compared to older chemotherapy regimens.

Especially in younger patients the restitution of menses after 2 years is greater than 90 %.²

However one third of the patients probably will be infertile after chemotherapy. The effects are more pronounced the older the patient and the longer the chemotherapy.

Data from the NSABBP B-30 trial (sequential versus concurrent ACT, doxorubicin-docetaxel in women with operable, node-positive, early stage breast cancer) amenorrhoe in premenopausal women was associated with improved disease-free and overall survival regardless of treatment, in particular when the tumor was ER-positive.^{3,4} The dose of drug delivered was not a key factor explaining the differences.⁴

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(Therapy Related) Fatigue (12/20)

Further information:

Fatigue is a common side effect during and after antineoplastic therapy. Especially in breast cancer incidence of moderate to severe fatigue ranges between 30 and as high as 60% (Lawrence 2004, Blaney 2012). This symptom is typically under-reported and under-treated and might adversely affect quality of life (Bower, 2008). Studies of long-term breast cancer survivors suggest that approximately one quarter to one third experience persistent fatigue for up to 10 years after cancer diagnosis (Bower et al, 2006).

Several factors are thought to contribute to cancer-related fatigue, including direct effects of cancer, adverse effects of cancer treatment, psychosocial factors, comorbid physical symptoms, and comorbid medical conditions. Anemia might contribute to a subset of cancer patients presenting with fatigue (Cella et al, 2004). Recent studies suggest an inflammatory basis for persistent fatigue in breast cancer survivors like increased NF- κ B and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue (Bower et al, 2010).

Behavioral and psychological interventions (Stanton et al, 2005) as well as physical exercise (McNeely et al, 2006, Bower et al, 2011) have demonstrated efficacy in reducing fatigue among breast cancer patients and survivors. It was shown in a meta-analysis by the Cochrane Collaboration that psychosocial interventions specifically addressing fatigue proved efficient (Goedendorp et al, 2009) and the same authors reported a randomized controlled trial showing that cognitive behavioural therapy was effective in reducing cancer-related fatigue. Contrary to what was expected, physical activity did not mediate the effect of cognitive behavioural therapy on fatigue in this study (Goedendorp et al, 2010). Another Cochrane Collaboration meta-analysis for physical exercise and fatigue only found statistically non-significant improvements for participants in the exercise intervention groups compared to control (non-exercising) groups. These authors concluded that improvements in fatigue were ambiguous and that strategies for behaviour change should underpin these interventions (Markes et al, 2006). In terms of pharmacological treatments for fatigue in a palliative setting, a study using methylphenidate (Ritalin™) in 112 cancer patients showed that this medication was not significantly superior to placebo after 1 week of treatment (Bruer et al, 2006). However, a significant effect of methylphenidate against cancer-related fatigue was confirmed in a meta-analysis performed by the Cochrane Collaboration (Peuckmann-Post et al, 2010). However the effectiveness of glucocorticoids, which are used broadly in daily praxis, has not yet been evaluated.

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Fatigue is frequently present...

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(Therapy Associated) Sleeping disturbance (13/20)

Further information:

Sleep disturbances are a common problem of breast cancer patients during and after therapy (20-70%) leading to disruption in women's quality of life and general ability to function (Bower, 2008; Savard et al, 2001; Ancoli-Israel et al, 2006). In a recently published study examining 823 cancer patients treated with chemotherapy, it was shown that 43% of the patients met the criteria for insomnia syndrome. Insomnia was approximately three times higher than the proportions reported in the general population. 60% of the patient sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (Palesh et al, 2010). Comorbidity, evening fatigue, and depressive symptoms predicted baseline levels of subjective sleep disturbance, and depressive symptoms predicted the trajectory of subjective sleep disturbance (Dhruva et al 2012).
E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R24#R24New data suggest that sleep disturbances, fatigue and depression may stem from distinct TNF-a mediated inflammatory processes, especially found in chemotherapy treated patients (Bower et al, 2011, Liu et al 2012).

Empirical studies of benzodiazepines and benzodiazepine receptor antagonists indicate that they are effective in improving various aspects of sleep, although no trials have evaluated the efficacy of these medications in cancer populations. Behavioral therapies have demonstrated efficacy in the treatment of insomnia, including insomnia secondary to medical conditions, supporting their use among breast cancer patients (Berger et al, 2009). Comparative studies have shown that behavioral therapies are at least as effective and longer lasting than pharmacotherapy in treating insomnia (McChargue DE et al 2012; Berger et al. 2009). Indeed, a randomized controlled trial of behavioural therapy for women with insomnia caused or exacerbated by breast cancer found significant improvement in subjective sleep complaints, as well as improvements in mood and quality of life (Savard et al, 2005).

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(Therapy Associated) Depression (14/20)

Further information:

Depression is an often reported adverse event in breast cancer patients. The majority of studies find that 20-30% of breast cancer patients experience elevated depressive episodes (Bower, 2008), even though the occurrence of a major depressive disorder might be lower. Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time. Depression negatively affects quality of life and there is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients (Gallo et al, 2007). The occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen (Bardwell et al, 2006). Depressed mood is correlated with fatigue and sleep disturbance in the context of breast cancer. In terms of treatment psychological interventions seem to be most effective distressed patients even though these interventions do not prolong survival. Regular exercise participation and tea consumption were shown in a population-based cohort study from Shanghai to play an important role in the prevention of depression among breast cancer survivors (Chen et al, 2010). Antidepressants have also shown to improve depression, in particular paroxetine has been shown to be effective in reducing depressive symptoms in breast cancer patients, even among those who were not depressed at study entry.

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Statements 1-4

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(Therapy Associated) Cognitive Impairment (15/20)

Further information

Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al, 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al, 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al, 2005).
E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R122#R122 Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al, 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al, 2010).

The biologic base for these changes is unclear. However, there are several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms (Ahles et al, 2007).

Cognitive behavioral therapy might lead to significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups (Ferguson et al, 2007). Other potential treatment approaches include methylphenidate, which has been used to improve cognitive

function in patients with advanced cancer. E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R130#R130

E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R110#R110

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Side-effects and Toxicity of Endocrine Agents I (16 /20)

Further information:

In a metaanalysis on 19.818 pts. treated with 3rd generation aromatase inhibitors the risk of developing cardiovascular adverse events was slightly higher in comparison to tamoxifen with an RR of 1.34 translating into a minimal risk of 0.5%. (Cuppone F et al 2008)

In an actual systematic review and metaanalysis of 30.023 patients in 7 trials comparing aromatase inhibitors with tamoxifen, the increased risk for developing cardiovascular disease (OR=1.26) for aromatase inhibitors was confirmed, as well as the occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

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Side-Effects and Toxicity – of Bone Modifying Agents (BMA, Bisphosphonates, Denosumab) (17/20)

Further information:

A recently published randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases. In terms of toxicity rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; $P = .39$) (Stopeck et al, 2010). In a pooled analysis of three randomized phase III trials of denosumab versus zoledronic acid in patients treated for metastatic cancer this occurrence rate for denosumab was confirmed with 1.67% (RR= 1,61) (Van den Wyngaert et al, 2011).

Although there amounting data, that bisphosphonates might have anticancer benefits for older postmenopausal women, the routine use of bisphosphonates as adjuvant treatment for patients with early breast cancer is not recommended (Paterson et al 2012; Wong et al 2012).

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Paterson AH, Anderson SJ, Lembersky BC, Fehrenbacher L, Falkson CI, King KM, Weir LM, Brufsky AM, Dakhil S, Lad T, Baez-Diaz L, Gralow JR, Robidoux A, Perez EA, Zheng P, Geyer CE Jr, Swain SM, Costantino JP, Mamounas EP, Wolmark N.: Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and

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Acute phase rea

Gastrointestinal side effects...

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Recommendations for Precautions to Prevent ONJ (18/20)

Further information:

The reported incidence of osteonecrosis of the jaw (ONJ) ranges from 0.94% to 18.6%. A study with 1,621 patients who received 29,006 intravenous doses of BP, given monthly reported an crude ONJ incidence of 8.5%, 3.1%, and 4.9% in patients with multiple myeloma, breast cancer, and prostate cancer, respectively. Patients with breast cancer demonstrated a reduced risk for ONJ development, which turned out to be non-significant after adjustment for other variables. Multivariate analysis demonstrated that use of dentures (aOR = 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR = 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR = 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR = 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development. Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP. In conclusion, validated dental extractions and use of dentures are risk factors for ONJ development. Ibandronate and pamidronate at the dosages and frequency used in this study seem to exhibit a safer drug profile concerning ONJ complication; however, randomized controlled trials are needed to validate these results. Before initiation of a bisphosphonate, patients should have a comprehensive dental examination.

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Frequent Side Effects of Bisphosphonate Treatment (19/20)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 17-18/20!

Key-Toxicity – Small Molecules / Antibodies (20/20)

Further information:

In the HERA trial, the incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% v 0.0%; confirmed significant LVEF decreases, 3.6% v 0.6%) In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery; of these 59 patients, 52 were considered by the cardiac advisory board (CAB) to have a favorable outcome from the cardiac end point. The incidence of cardiac end points remains low even after longer-term follow-up and the majority of cardiac events resolved (Procter et al, 2010).

In the NSABP B-31- and NCCTG 9831-trial trastuzumab-treated patients had a 2.0% incidence of symptomatic heart failure events compared with 0.45% in the chemotherapy-alone arm. Complete or partial recovery was observed in 86.1% of trastuzumab-treated patients with symptomatic heart failure events after cessation of trastuzumab. Independent predictors for cardiac events were age older than 50 years, a low ejection fraction at the start of paclitaxel treatment, and trastuzumab treatment. The majority of these patients recover with appropriate treatment (Russell et al, 2010).

The usefulness of troponin I in the identification of patients at risk for trastuzumab induced cardiotoxicity (TIC) and in the prediction of LVEF recovery was investigated in 251 women treated with trastuzumab. TNI was measured before and after each trastuzumab cycle. TIC occurred more frequent in patients with troponin elevation (TNI+; 62% v 5%; $P < .001$). Thus, Troponin increase identifies trastuzumab-treated patients who are at risk for cardiotoxicity and are unlikely to recover from cardiac dysfunction despite HF therapy.

In the Phase III trial of Capecitabine with or without the oral tyrosine-kinase-inhibitor lapatinib which led to the approval of lapatinib in advanced HER-2 positive breast cancer, asymptomatic cardiac events were identified in four women in the combination-therapy group and in one woman in the monotherapy group. All of these events in the combination-therapy group were considered to be related to treatment, and all women had an LVEF value that was at or above the lower limit of the normal range on subsequent assessment.

The most common adverse events were diarrhea, the hand–foot syndrome, nausea, vomiting, fatigue, and rash that was distinct from the hand–foot syndrome. Most adverse events were grade 1, 2, or 3. Grade 4 diarrhea occurred in two women in the combination-therapy group (1%). One case each of grade 4 fatigue, headache, and dizziness was reported in the monotherapy group. Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy.

A systematic review and meta-analysis of five randomized phase III clinical trials that used bevacizumab alone or in combination with chemotherapy in metastatic breast cancer showed a statistically significant bevacizumab associated increased risk for proteinuria (OR=27.68), hypertension (OR=12.76), left ventricular dysfunction (OR=2.25) and hemorrhagic events (OR=4.07), while no increased incidence was found for gastrointestinal perforation, vascular or fatal events and febrile neutropenia, respectively

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Von Minckwitz G, Eidtmann H, Loibl S et al: Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. *Ann Oncol* 22:301-306, 2011

Sherill B, Amonkar MM, Sherif B et al: Quality of life in hormone receptor-positive Her2-positive metastatic breast cancer patients during treatment with letrozole alone or in combination with lapatinib. *Oncologist* 15:944-953, 2010

Cameron D, Casey M, Olicka C et al: Lapatinib plus capecitabine in women with Her2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. *Oncologist* 15:924-934, 2010

Geyer CE, Forster J, Lindquist D; et al: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 355:2733-2743, 2006

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Drucker AM, Wu S, Dang CT, Lacouture ME.: Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. *Breast Cancer Res Treat.* 2012 Sep;135(2):347-54.

Baselga J, Cortes J, Kim S-B et al. Pertuzumab plus Trastuzumab plus Docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366:109-119

T-DMI ...

Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012 Nov 8;367(19):1783-91.

Everolimus: Baselga J, Campone M, Rugo H et al. Everolimus in postmenopausal hormone receptor positive advanced breast cancer. *N Engl J Med* 2012;366: 520-529

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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➤ **Version 2002:**
Diel

➤ **Versions 2003–2013:**
**Bauerfeind / Bischoff / Costa / Dall / Diel
/ Fersis / Hanf / Heinrich / Jackisch /
von Minckwitz / Oberhoff / Rody /
Schaller / Scharl / Schütz**

➤ **Version 2014:**

➤ **Schmidt / Möbus**

Further
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References

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Guideline Spectrum

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients

We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language

Special emphasis is put on aspects concerning breast cancer patients

**In the German environment, special interest is earned by the publications of the „Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG:
<http://www.onkosupport.de>“**

In preparation: multidisciplinary guidelines of the AWMF:

„Supportive Therapie bei onkologischen Patientinnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, planned release: 30.6.2015

„Palliativmedizin“, announced 03.12.2010, planned release 31.03.2014

Erythropoiesis-stimulating agents (ESAs)

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- **Indicated in asymptomatic anaemia**
 - In dose-dense / dose-escalated CT (iddETC)
- **Indicated in symptomatic anaemia**
 - In the adjuvant setting
 - In the neoadjuvant/metastatic setting
- **Treatment and secondary prophylaxis of chemotherapy induced anemia (CIA)**
- **Improvement of outcome (DFS, OS)**
- **Treatment start at Hb-levels approaching < 10 g/dL**
- **Target Hb 11–12 g/dL**
- **Thromboembolic events are increased with ESAs**

**Oxford / AGO
LoE / GR**

| | | |
|-----------|----------|------------|
| 1a | B | - |
| 1b | A | + |
| 1b | A | + |
| 1a | A | +/- |
| 1a | A | + |
| 2b | B | -- |
| 1a | A | + |
| 1a | A | + |
| 1a | A | |

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Practical Use of ESAs

Oxford / AGO
LoE / GR

1b A ++

- **Epoetin α and Darbepoetin are equieffective**

- **Dose:**

- **Epoetin α : 150 IU/kg 3 x weekly s.c. or**

40.000 IU 1 x /week s.c.

1a A ++

- **Epoetin α : 80.000 IU q2w s.c. or**

120.000 IU q3w s.c.

1b B +

- **Darbepoetin: 2,25 μ g/kg s.c. weekly**

1b A ++

- **Darbepoetin: 500 μ g s.c. q3w**

1b A ++

- **Hb measurements weekly**

- **Dose reduction at Hb-increase > 1g/dl within 2 weeks**

- **Dose increase at Hb-increase < 1g/dl within 4-6 weeks**

- **In case of FID give IV iron supplementation**

1a B +

- **p.o. iron supplementation**

1a B +/-

- **STOP ESA-treatment in case of missing increases of Hb-levels after 9 weeks**

1b A ++

Relevant Guidelines

- Rodgers GM and Gilieath JA: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2013.
Available from: URL: <http://www.nccn.org>
- Rizzo JD et al: ASCO/ASH/Clinical Practice Guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 2010; 28: 4996–10

Prophylaxis of Infections

NB Rarely Applicable to Patients with Solid Tumors (e.g. BC)
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

**Oxford / AGO
LoE / GR**

| | | | |
|--|-----------|----------|------------|
| ➤ Avoidance of highly infection-risking behaviour or situations | 5 | D | + |
| ➤ Prophylactic treatment in low risk patients | 1a | B | - |
| ➤ Prophylactic treatment in high risk* patients (e.g. according to NCCN Guidelines) with | | | |
| ➤ Antibiotics | 1a | A | ++ |
| ➤ Anti-fungal agents (triazole) | 1a | B | +/- |
| ➤ Virostatics in solid tumors | 5 | D | - |
| ➤ Granulocyte colony-stimulating factors | 1a | A | ++ |

*** High risk definition: estimated duration of neutropenia $< 100/\mu\text{l} \geq 7\text{d}$**

Relevant Guidelines

- Flowers et al: Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 31: 794-810, 2013

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Mucositis

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

➤ **Desinfecting / antiphlogistic measures:**

Mouth rinsing with infusions of camomile or salvia, extracts of camomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol

➤ **Mucosa protecting measures (during / after application of chemotherapy):**

Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-Mundgel®) every 4–6 hrs for HD-methotrexate: do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!). Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.

➤ **Local antimycotic treatment:**

Amphotericine B, nystatine, fluconazole

➤ **Local antiviral treatment**

Aminoquinuride / tetracaine-HCl , Aciclovir®

➤ **Local anaesthesia:**

Benzocaine PO

Granulocyte Colony-stimulating Factors

Oxford / AGO
LoE / GR

- **Primary prophylaxis for expected febrile neutropenia (FNP)**
 - **If expected risk for FNP 10–20%**
 - **In case of individual risk factors**

1b B +/-

3b C +
 - **If expected risk for FNP >20% (e.g. DAC, dose-dense CT)**

1a A ++
- **Secondary prophylaxis during chemotherapy (previous FNP or neutropenia grade IV > 7 days)**

1b B ++
- **Therapeutic usage for FNP**

1a A +/-
- **Start related to chemotherapy and duration**
 - **Pegfilgrastim day 2**

1b A ++
 - **Lipegfilgrastim day 2**

1b B +
 - **Filgrastim/Lenograstim from day 2–3 until ANC > 2–3 x 10⁹**

1b A ++

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Relevant Guidelines

- Crawford et al: Myeloid Growth Factors. J Natl Compr Canc Netw:1266-1290, 2013
- Smith et al: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors. J Clin Oncol 24:3187-3205, 2006
- Crawford et al: Hematopoietic growth factors. Ann Oncol 21 (suppl 5): v248-v251, 2010

Management of Febrile Neutropenia

c.f. Recommendations by Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)

Definition (oral temperature of $>38.5^{\circ}\text{C}$ or two consecutive readings of $>38^{\circ}\text{C}$

for 2 h in a patient with an ANC of <500 cells/mm³ or expected to fall to <500 cells/mm³)

**Oxford / AGO
LoE / GR**

| | | | |
|---|-----------|----------|------------|
| ➤ Clinical examination | 5 | D | ++ |
| ➤ Daily evaluation | 5 | D | ++ |
| ➤ Hospitalization of high risk patients | 1b | A | ++ |
| ➤ Homecare in low risk patients | 1b | A | + |
| ➤ Differential blood count | 5 | D | ++ |
| ➤ Blood cultures | 5 | D | ++ |
| ➤ Imaging of lungs | 3 | C | ++ |
| ➤ Immediate initial empiric antibiotic therapy | 1a | A | ++ |
| ➤ Empiric antifungal therapy 4–7d | | | |
| in case of failure of antibiotic therapy | 1b | A | ++ |
| ➤ G-CSF for treatment (not prophylactic) | 2b | B | +/- |

Calculated Antibiotic Therapy in FN

Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO)
www.dgho-infektionen.de
regularly issues such recommendations in German.

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Dexrazoxane

http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

**Oxford / AGO
LoE / GR**

➤ **Treatment of anthracycline extravasation**

2b B +

➤ **In combination with anthracyclines for cardiac protection**

1a B +/-

➤ **In cardiac risk patients**

➤ **Dexrazoxane**

1b B +

➤ **Consider alternative regimens (anthracycline-free, liposomal)**

5 D ++

Paravasation Dexrazoxane

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

**Otherwise or if treatment with dexrazoxane is not indicated,
following measures are recommended**

- 1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling**
- 2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to dry on air. The interval may be extended to 6 hours from day 4 onward.**

Antiemetic Therapy

<http://www.mascc.org/antiemetic-guidelines>

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- | | | | |
|---|-----------|----------|-----------|
| ➤ After assessment of emetic potential of chemotherapy protocol | 5 | D | ++ |
| ➤ Neurokinin-1-receptor-antagonists | 1b | A | ++ |
| ➤ Dexamethasone | 1a | A | ++ |
| ➤ 5-HT ₃ -antagonists | 1b | A | ++ |
| ➤ Metoclopramide | 3b | C | + |

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MASCC/ESMO Antiemetic Guideline 2011



Multinational Association of Supportive Care in Cancer

Organisation und Vorstand:

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Supportive Therapy

Antiemetics

| Wirkstoffgruppe | Substanz | Dosierung | Nebenwirkungen | Potenzial |
|---|-----------------------|---|--|-----------|
| Serotoninantagonisten | Ondansetron | 8 mg i.v., 2 x 4-8 mg p.o | Kopfschmerzen, Diarrhoe, Flushsymptomatik | sehr hoch |
| | Tropisetron | 5 mg i.v., 5 mg p.o. | Transaminasenanstieg | |
| | Granisetron | 1-3 mg i.v. | Darmatonie in hoher Dosierung | |
| | Palonosetron | 0, 25 mg i.v. | | |
| NK 1-Antagonisten | Aprepitant | 125 mg d1, 80 mg d 2-3 p.o. | Cytochrom-P-450- Aktivierung mit Dosisreduktion von Dexamethason (2 x 8 mg). Keine Kombination mit Astemizol, Terfenadin, Cisaprid | sehr hoch |
| | Fosaprepitant | 150 mg d1 i.v. | | |
| Dopaminantagonisten/ substituierte Benzamide | Metoclopramid | bis zu 120 mg/24h als Dauerinfusion od. als Tropfen | Dyskinesien (Antidot: Biperiden) | hoch |
| | Alizaprid | bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.) | Angstreaktion, Depressionen, Diarrhoe | |
| Phenothiazine/ Butyrophenone | Haloperidol | 1-3 mg 4 x/d | Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung | mäßig |
| Corticosteroide | Dexamethason | 8-20 mg i.v. 1-3 x/d | Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg | mäßig |
| | Prednisolon | 100-250 mg i.v. 1-3 x/d | | |
| Benzodiazepine | Diazepam Lorazepam | bis zu 20 mg/d 0,5-1,0 mg/d | Sedation, Atemdepression | gering |
| Antihistaminika | Dimenhydrinat | bis zu 3 x 50 mg/d | Sedation, Mundtrockenheit | gering |

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Analgesia

(See Specific Guidelines for Analgesia www.dgss.org)

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➤ **Non-opioids; WHO Step 1**

Diclofenac resinate, ibuprofene and / or metamizole, paracetamole

➤ **Mild opioids; WHO Step 2**

Tramadol (preferentially „retard“-formulations)
or tilidine / naloxone (also as „retard“-formulations)

➤ **Strong opioids; WHO Step 3**

Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as back-up levomethadone. The dose of opioids should be titrated step by step according to the analgetic effect.

➤ **Additional drugs – „adjuvants“**

Gabapentine, pregabalin, carbamazepine, amitriptyline, bisphosphonates

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Diarrhea

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➤ Adsorbent agents

- Carbo medicinalis; *caoline / pectine, Al-Mg-silicate hydrate*

➤ Analgetics, opioids

- Loperamide; *codeine, morphine IV, tinctura opii, butylscopolamine*

➤ Colitis pseudomembranosa

- Metronidazols *or (if not effective) vancomycine*

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References

Constipation

Important Side Effect of Opioid Treatment

➤ Swelling agents

- Psyllium, flaxseed (shredded)

➤ Osmotic laxatives

- Macrogol > Lactulose (Cochrane review **LoE 1a, AGO +**)
- Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate
- Sorbite

➤ Motility stimulating laxatives

- Sennae, Ricinus, Bisacodyl, sodium-picosulfate

➤ Emollients (Internal lubricants e.g. paraffin)

➤ Opioid-receptor-antagonists (in opioid-related constipation)

- Methylnaltrexone

Palliative Care

- “...expert consensus that **combined standard oncology care and palliative care** should be **considered early in the course of illness** for **any patient with metastatic cancer and/or high symptom burden.**”¹
- “Palliative care should be **initiated by the primary oncology team** and augmented by **collaboration** with an interdisciplinary team of palliative care experts.”²
- “Expert **palliative care**, including effective control of pain and other symptoms, **should be a priority.**”³

¹ Smith et al, J Clin Oncol 30 880-887, 2012

² Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012

³ Cardoso et al, Breast 21:242-252, 2012

Supportive Care (2/ 22)

No further information

No references

Guideline spectrum (3/22)

Further information:

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients

We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language.

Special emphasis is put on aspects concerning breast cancer patients.

In the German environment, special interest is earned by the publications of Arbeitsgem. Supportive Maßnahmen in der Onkologie , Rehabilitation und Sozialmedizin der DKG: <http://www.onkosupport.de>

In preparation: multidisciplinary guideline of the AWMF: „Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, planned release: 30.6.2015

No references

Erythropoiesis-Stimulating Agents (ESAs) (4/22)

Further information:

Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa were indicated for use in chemotherapy-induced anemia to achieve target hemoglobin (Hb) levels of approximately 12 grams per deciliter (gm per dL), and treatment was to be withheld if Hb exceeded 13 gm per dL. In March 2007, the FDA changed the labeling of the ESAs to add boxed warnings, updated in November 2007, to include the following key points: (a) ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy; (b) treatment with ESAs should be stopped when chemotherapy ends; and (c) dosing ESAs to an Hb target of 12 gm per dL or greater has resulted in more rapid cancer progression or shortened overall survival in patients with breast, head and neck, lymphoid, cervical, and non-small cell lung malignancies. In January 2008, the FDA specified that the increased risk of more rapid tumor growth or shortened survival was associated with ESAs when "administered in an attempt to achieve a Hb level of 12 gm per dL or greater, although many patients did not reach that level." A new black-box warning regarding this association was added to the labels of the ESAs in March 2008, and the FDA mandated further label changes on July 30, 2008, that ESA therapy should not be initiated in patients receiving chemotherapy at Hb levels of 10 gm per dL or higher.

OBJECTIVE: To (a) assess the prevalence and predictors of ESA administrations at Hb levels above 12 gm per dL among patients with a diagnosis of solid or hematologic cancer or myelodysplastic syndrome who began their first regimen of conventional myelosuppressive chemotherapy between 2002 and 2006, and (b) describe patterns of ESA treatment subsequent to the first ESA administration at Hb above 12 gm per dL.

In 2012 a Cochrane review was published by Tonia et al., extracting data from a total of 91 trials with 20,102 participants to perform a systematic review, concluding that ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.

References:

- Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. :Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: A descriptive study of a large outpatient oncology practice database, 2000-2007. Clin Ther. 2009;31P2:2416-2432.
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- Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, Hyde C, Engert A, Bohlius J. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD003407. DOI: 10.1002/14651858.CD003407.pub5.

Further references:

Statement: An increased mortality and tumor progression by the use of ESF can not be safely ruled out

1. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103234s5199lbl.pdf
2. PREPARE-Studie, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116830.htm>
3. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E, Maintaining normal hemoglobin

levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study, J Clin Oncol. 2005 Sep 1;23(25):5960-72

Relevant Guidelines:

J Oncol Pract. 2010 Nov;6(6):317-20. doi: 10.1200/JOP.2010.000132.

American society of clinical oncology/american society of hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S.

Rizzo JD et al: ASCO/ASH/clinical practise guideline/epoetin and darbepoetin/adult patients with cancer. J Clin Oncol 2010; 28: 4996–10

Aapro MS, Link H: Update 09/2007/EORTC guidelines/anemia management/erythro-poiesisstimulating agents. Oncologist 2008; 13 (suppl 3): 33–6; Aktualisierung 2012 in Vorbereitung

Rodgers GM: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2011
Available from: URL: <http://www.nccn.org>

Practical Use of ESAs (5/22)

Further information:

For practical use refer to relevant practice guidelines

The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient's clinical circumstances and preferences.

References:

Rizzo JD et al: ASCO/ASH/clinical practise guideline/epoetin and darbepoetin/adult patients with cancer. J Clin Oncol 2010; 28: 4996–10

Relevant guidelines (6/22)

No further information

References:

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Rizzo JD et al: ASCO/ASH/Clinical Practice Guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 2010; 28: 4996–10

Prophylaxis of Infection (7/22)

Further information:

According to relevant guidelines, antibiotic prophylaxis of asymptomatic patients under chemotherapy should be restricted to high risk cases: one selective criterion could be expected duration of neutropenia of greater than 10 days (NCCN). (ASCO absolute neutrophil count < 100/ μ l > 7days) N.B.: Standard chemotherapy protocols such as used in breast cancer patients do not regularly justify antibiotic prophylaxis.

The use of oral prophylactic antibiotics in patients with neutropenia is controversial and not recommended by the Australian Consensus Guidelines 2011 Steering Committee because of a lack of evidence showing a reduction in mortality and concerns that such practice promotes antimicrobial resistance. Recent evidence has demonstrated non-significant but consistent, improvement in all-cause mortality when fluoroquinolones (FQs) are used as primary prophylaxis. However, the consensus was that this evidence was not strong enough to recommend prophylaxis.

Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179-1187: In a meta-analysis that evaluated 18 trials (N=1408) in which fluoroquinolones were compared to either placebo or TMP/SMX, fluoroquinolone prophylaxis significantly reduced the incidence of Gram-negative infections by about 80% compared with those without prophylaxis (relative risk=0.21; 95% CI, 0.12-0.37), leading to an overall reduction in total infections.

Latest update: in the latest ASCO Guideline on Antimicrobial Prophylaxis and Outpatient Management... (2013) the use of antimicrobial prophylaxis is only recommended for patients expected to have 100 neutrophils/ L for 7 days, unless other factors increase risks for complications or mortality to similar levels. The authors clearly state, that chemotherapy for solid tumors rarely leads to the mentioned conditions. An oral fluoroquinolone is preferred for antibacterial prophylaxis and an oral triazole for antifungal prophylaxis. The guideline encourages the use of myeloid growth factor prophylaxis to render antimicrobial prophylaxis unnecessary.

Interventions such as footwear exchange, protected environments, respiratory or surgical masks, neutropenic diet, or nutritional supplements are not recommended because evidence is lacking of clinical benefits to patients from their use

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Antimicrobial Prophylaxis and Outpatient Management of
Fever and Neutropenia in Adults Treated for Malignancy:

American Society of Clinical Oncology Clinical Practice Guideline

*Christopher R. Flowers, Jerome Seidenfeld, Eric J. Bow, Clare Karten, Charise Gleason, Douglas K. Hawley,
Nicole M. Kuderer, Amelia A. Langston, Kieren A. Marr, Kenneth V.I. Rolston, and Scott D. Ramsey*

ASCO Practice Guideline „Antimicrobial Prophylaxis...” 2013 The latest version is at

<http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.45.8661>

Published Ahead of Print on January 14, 2013 as 10.1200/JCO.2012.45.8661

Relevant guidelines (8/22)

No further information

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Mucositis (9/22)

Further information:

„Mukositis kann als schwere und dosislimitierende Nebenwirkung bei Chemotherapie und Strahlentherapie von Malignomen auftreten. In Ausprägungen von Grad III und IV gefährdet die Mukositis nicht nur das kurative Therapieziel durch möglicherweise notwendige Therapieverschiebungen oder Therapieabbrüche, sondern sie beeinträchtigt auch erheblich die Lebensqualität der Patienten. Außerdem stellt die Mukositis bei neutropenischen Patienten einen zusätzlichen Risikofaktor für eine Sepsis dar, die mit erhöhter Letalität verbunden ist.

Die Pathogenese der Mukositis ist nicht vollständig geklärt. Diagnostik, Therapie und Prophylaxe werden bisher nicht standardisiert durchgeführt und sind hauptsächlich auf die Symptomkontrolle ausgerichtet.“

References:

Relevant Guidelines

[http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006\(dtV\).pdf](http://www.mascc.org/assets/documents/MukositisGuidelinesMASCC2006(dtV).pdf)

Granulocyte Colony-stimulating Factors (10/22)

Further information:

The ability to deliver the planned dose and intensity of chemotherapy (the amount of drug administered/unit of time) is important for tumor control and survival. In clinical practice, neutropenic events are the main limiting factors towards achieving this aim. Furthermore, severe neutropenia accompanied by fever, so called „febrile neutropenia (FN)“, is the most serious manifestation of neutropenia usually requiring hospitalization and intravenous antibiotics. Without stringent management FN is associated with significant morbidity and mortality. The primary use of recombinant granulocyte colony-stimulating factors has reduced the incidence of febrile neutropenia during dose-dense adjuvant/neoadjuvant chemotherapy programs for breast cancer.

In 2012, a Cochrane review sought to assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer.

The authors concluded that „In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefit in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects.“

In a comparative effectiveness study, pegfilgrastim prophylaxis was associated with a reduced risk of neutropenia-related or all-cause hospitalization relative to filgrastim prophylaxis.

A recent study demonstrated in high risk breast cancer that 6 mg lipegfilgrastim, a novel glyco-pegylated granulocyte-colony stimulating factor, was as effective as pegfilgrastim in reducing neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy.

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NCCN:

NCCN Guidelines Version 1.2012 Panel Members Myeloid Growth Factors

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Stimulation der Granulopoese mit G-CSF

Kurzgefasste interdisziplinäre Leitlinie 2008 der Deutschen Krebsgesellschaft, die unter der Verantwortung der ASO bzw. ASORS erstellt wurde. http://www.krebsgesellschaft.de/download/ll_o_04.pdf

Relevant guidelines (11/22)

No further information

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Management of Febrile Neutropenia (12/22)

Further information:

The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines.

A Cochrane review sought to evaluate the safety and effectiveness of adding colony stimulating factors (CSF) to antibiotic therapy when treating febrile neutropenia caused by cancer chemotherapy. The authors looked for all randomized controlled trials (RCTs) that compare CSF plus antibiotics versus antibiotics alone for the treatment of established febrile neutropenia in adults and children. After inclusion of 13 studies the authors concluded, that „ the use of CSF in patients with febrile neutropenia due to cancer chemotherapy does not affect overall mortality, but reduces the amount of time spent in hospital and the neutrophil recovery period. It was not clear whether CSF has an effect on infection-related mortality.“

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NCCN:

NCCN Guidelines Version 1.2012 Panel Members Myeloid Growth Factors

http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf

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Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)

Calculated Antibiotic Therapy in FN (13/22)

Further information:

The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines. Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

References:

Relevant practice guidelines:

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)

Dexrazoxane (14/22)

Further information:

Anthracyclines are among the most active chemotherapeutic agents in cancer treatment. Although infrequent, cumulative dose-dependent cardiotoxicity is nevertheless a significant side effect of this therapy resulting in reduced cardiac reserve or even frank cardiac failure. Although used in several types of malignancy, anthracyclines are most commonly used in breast cancer treatment. Importantly, recent advances have also seen the increasing use of another cardiotoxic agent, the monoclonal antibody trastuzumab, both in the metastatic as well as in the adjuvant breast cancer setting. A great number of studies review and discusses the relationship of cardiotoxicity and anthracycline use, particularly in the breast cancer setting, and explores available treatment options for the anthracycline-treated patients based on evidence from recent Phase III trials.

Dexrazoxane is not recommended for routine use in breast cancer (BC) in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Consider use with metastatic BC and other malignancies, for patients who have received more than 300 mg/m² doxorubicin who may benefit from continued doxorubicin-containing therapy. Cardiac monitoring should continue in patients receiving doxorubicin.

A Cochrane review investigated Cardioprotective interventions for cancer patients receiving anthracyclines and concluded: ...“The nine included studies of dexrazoxane enrolled 1403 patients. The meta-analysis of dexrazoxane showed a statistically significant benefit in favour of dexrazoxane for the occurrence of heart failure (Relative Risk (RR) 0.29, 95% CI 0.20 to 0.41). No evidence was found for a difference in response rate or survival between the dexrazoxane and control group. Only for one adverse effect (abnormal white blood cell count at nadir) a difference in favour of the control group was identified.“

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Paravasation Dexrazoxane (15/22)

Further information:

Although indicated and approved for cardioprotection, dexrazoxane has been suggested as being helpful in the case of anthracyclin paravasation. The agent is administered systemically.

References:

Relevant practice guideline

Zytostatika-induzierte Paravasate - Empfehlungen zu Diagnose, Prophylaxe und Therapie [PDF-Datei]

Arbeitsversion der ASORS Paravasate-Guidelines (Stand April 2010)

Maike de Wit, Petra Ortner, Hans-Peter Lipp, Jalid Sehouli, Michael Untch, Markus Ruhnke, Regine Mayer-Steinacker, Carsten Bokemeyer, Karin Jordan

download: http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

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Prävention, Diagnostik und Therapie der zytostatikaassoziierten Paravasation - Was tun wenn's brennt?

Im Focus Onkologie 2010;6:50-55.

Antiemetic Therapy (16/22)

Further information:

Nausea and vomiting are two of the most severe problems for patients treated with chemotherapy. Until the late 1970s, nausea and vomiting induced by chemotherapy was an almost neglected research area. With the introduction of cisplatin, the cytotoxin with the highest emetic potential, research was stimulated and has now resulted in the development of two new classes of antiemetics, the serotonin and neurokinin antagonists. A large number of trials have fine-tuned antiemetic therapy and made evidence-based recommendations possible for the majority of patients receiving chemotherapy. A systematic Review summarizes recommendations from the evidence-based guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC).

The combination of ondansetron, dexamethasone and aprepitant is able to protect 66–78% of patients from emesis and 48–49% from nausea during the first cycle of cisplatin-based chemotherapy. In a subsequent trial, single-dose intravenous fosaprepitant (150 mg) given with ondansetron and dexamethasone was noninferior to standard 3-day oral aprepitant in preventing CINV during OP and DP.

In women receiving cyclophosphamide/anthracycline-based chemotherapy for breast cancer, the corresponding figures are 76% and 33%. In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to aprepitant but instead had similar efficacy and toxicity in preventing delayed emesis.

New antiemetics have been highly successful in the prophylaxis of emesis, but are less effective in the prevention of nausea. There is, therefore, a particular interest in initiating trials to investigate agents with potential anti-nausea effect, such as olanzapine. Guidelines such as the MASCC antiemetic guidelines are only useful if they are continuously updated and implemented in the daily clinic. To encourage implementation, the MASCC guidelines have been translated into several languages, are updated every 6 months (as new data arise), and are always accessible on the MASCC website.

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Relevant Guidelines

<http://www.mascc.org/antiemetic-guidelines>

Antiemetische Prophylaxe gemäß MASCC- und ASCO-Guidelines
[PDF-Datei (auf www.krebsgesellschaft.de)]

Kurzgefasste interdisziplinäre Leitlinie 2008 der Deutschen Krebsgesellschaft, die unter der Verantwortung der ASO bzw. ASORS erstellt wurde.

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Supportive Therapie: Antiemetic Guideline MASCC (17/22)

No further information

No references

Supportive Therapie: Antiemetics (18/22)

No further information

No references

Analgesia (19/22)

No further information

References:

Relevant guidelines

Deutsche Gesellschaft zum Studium des Schmerzes, www.dgss.org

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Diarrhea (20/22)

No further information

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Constipation (21/22)

Further information:

Constipation is not infrequently encountered during chemotherapy. Particularly around the time in autumn and winter, when indoor heating begins and air humidity is consequentially reduced. Sufficient fluid uptake should be encountered by treating health care providers. Opioid therapy usually results in constipation and regular digestion should always be aimed at.

A Cochrane meta-analysis investigated differential efficacy of different agents, the authors concluded, that „The findings of our work indicate that Polyethylene glycol is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. On subgroup analysis, this is seen in both adults and children, except for relief of abdominal pain. Polyethylene Glycol should be used in preference to Lactulose in the treatment of Chronic Constipation.“

More recently, the use of parenteral methylnaltrexone for the management of constipation in palliative care patients was evaluated. Subcutaneous methylnaltrexone; an opioid-receptor antagonist, is now licensed for the treatment of opioid-induced constipation in palliative care when response to usual laxative therapy is insufficient. The authors concluded, that „Here it found that subcutaneous methylnaltrexone is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives have failed. However, the safety of this product is not fully evaluated. Large, rigorous, independent trials are needed.“

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Palliative Care (22/22)

Further information

Growing evidence and increasing awareness in international recommendations underlines the relevance of combined standard oncology care and palliative care. This should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden. It is evident that the access to palliative care, including effective control of pain and other symptoms, is important in the treatment of metastatic breast cancer patients.

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Diagnosis And Treatment Of Patients With Primary And Metastatic Breast Cancer

Breast Cancer: Specific Situations

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➤ **Versions 2005-2013:**

**Dall / Fersis / Friedrich / Gerber / Göhring /
Harbeck / Huober / Janni / Loibl / Lück / Lux /
Maass / Mundhenke / Oberhoff / Rody /
Scharl**

➤ **Version 2014:**
Fehm / Schneeweiss

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- **Young patients**
- **Pregnancy-associated BC**
- **Elderly patients**
- **Male patients**
- **Inflammatory BC**
- **Occult Primary [Carcinoma of unknown primary (CUP)]**
- **Paget's disease**
- **Malignant Phyllodes Tumor**
- **Sarcomas**

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Breast Cancer in Young Women ≤ 35 Years

Oxford / AGO
LoE / GR

| | | | |
|--|-----------|----------|-------------|
| ➤ Aggressive biological behavior | 2a | B | |
| ➤ Benefit from chemotherapy | 1b | A | ++ |
| ➤ Benefit from endocrine therapy | 1b | A | ++ |
| ➤ Endocrine therapy (TAM) if possible 5-10 y | 1b | B | ++ |
| ➤ Benefit from HER2 targeted therapy | 2b | B | ++ |
| ➤ Benefit from CT induced temporary amenorrhoea | 2b | B | +/-* |
| GnRHa as ovary protection 2 weeks prior CT | 1a | A | -* |
| ➤ Surgery like ≥ 35 y (in particular BCT) | 2b | B | + |
| ➤ Stage II–III benefit from PMRT | 2b | C | + |
| ➤ Genetic and fertility counseling | 2b | B | ++ |

* Study participation recommended

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Breast Cancer During Pregnancy* or Breast Feeding

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LoE / GR

- **Breast imaging & biopsy like in non-pregnant**
- **Staging: ultrasound, chest X-ray if indicated**
- **Surgery like in non-pregnant patients**
- **Sentinel node excision (technetium only)**

4 C ++

5 D +/-

4 C ++

4 C +

SNE during 1st trimester

5 D +/-

- **Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs**

4 C ++

- **Blue dye (has not been tested in pregnant animals or humans)**

4 C --

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Breast Cancer During Pregnancy*

Oxford / AGO

LoE / GR

| | | | |
|--|----|---|----|
| ➤ Radiation therapy during pregnancy | 4 | C | - |
| ➤ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant) | | | ++ |
| ➤ AC, FAC (FEC) | 2b | B | ++ |
| ➤ Taxanes | 2b | B | + |
| ➤ MTX (e.g. CMF) | 4 | D | -- |
| ➤ Endocrine treatment | 4 | D | -- |
| ➤ HER2-neu targeted treatment | 3a | C | -- |
| ➤ Bisphosphonates | 4 | D | - |

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Breast Cancer During Pregnancy*

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LoE / GR

- **Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)** **2b C ++**
- **Termination of pregnancy does not improve maternal outcome** **3b C**
- **Delivery mode like in healthy women, avoid delivery ≤ 3 weeks from prior chemotherapy** **4 C ++**
- **If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities** **5 D ++**

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Pregnancy Associated Breast Cancer*: Outcome

**Oxford
LoE**

BC during pregnancy / lactation

- Adequate treatment is essential

3a

Pregnancy and lactation after BC

- Outcome not compromised

3a

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Geriatric Assessment

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- **No specific algorithm is available**
- **Ability to tolerate treatment varies greatly („functional reserve“)**
- **Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals**
 - Physical, mental, and psycho-social health
 - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
 - Living arrangements, social network, access to support services
- **Assessment tools:**
 - **Charlson Comorbidity Index** (widely used; good predictor over a 10-year period)
 - **12 prognostic indicators to estimate 4-year mortality risk**
 - **Short screening tests** (more qualitative evaluation)
 - **IADL** (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8

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Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

Oxford / AGO LoE / GR

- **Geriatric assessment**
- **Treatment according to standard**
 - **Surgery similar to „younger“ age**
 - **Endocrine treatment (endocrine resp.)**
 - **Chemotherapy**
 - **< 70 years**
 - **> 70 years (especially N+, ER/PgR-)**
 - **Radiotherapy**
 - **Omit Radiotherapy after BCT in low risk with endocrine treatment****
 - **Trastuzumab**

2b B ++

2a C ++

2b B ++

1a A ++

1a A +

2a C +*

1a A +

1b(a) B +

2b C +

*Study participation recommended

**Population > 70 y, hormone receptor positive and if endocrine therapy is planned (CAVE: increased risk local recurrence)

Treatment for Frail Patients

(Life Expectancy <5 yrs, Substantial Comorbidities)

Oxford / AGO
LoE / GR

- | | | | |
|--|-------------------------|----------|-----------|
| ➤ Reduced standard treatment | 2b | C | ++ |
| ➤ Options extrapolated from trials in elderly: | | | |
| ➤ No breast surgery (consider endocrine options) | 2b | C | + |
| ➤ No axillary clearing (≥ 60 y, cN0, Rec pos) | 2b | B | + |
| ➤ No radiotherapy (≥ 65 y, pT1, pN0, Rec pos) | 1b^(a) | B | ++ |
| ➤ Hypofractionated radiotherapy | 2b | C | + |
| ➤ No chemotherapy >70 years and negative risk-benefit analysis | 2b | C | + |

Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

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- **Diagnostic work-up as in women**
 - Mammography
 - Ultrasound
- **Standard-surgery: Mastectomy**
 - BCT may be an option (tumor breast relation)
 - Sentinel-node excision (SNE)
- **Radiotherapy as in women
(consider tumor breast relation!)**
- **Genetic counselling if one additional
relative affected (breast/ovarian cancer)**
- **Screening for 2nd malignancies
according to guidelines**

**Oxford / AGO
LoE / GR**

| | | |
|------------|----------|------------|
| 4 | C | + |
| 3b | C | +/- |
| 2b | B | ++ |
| 4 | C | ++* |
| 4 | C | ++* |
| 2b | B | + |
| 4 | C | + |
| 2b | B | ++ |
| GCP | | ++ |

***Participation in register study recommended**

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Male Breast Cancer: Systemic Therapy

Oxford / AGO LoE / GR

- **Adjuvant chemotherapy as in women**
- **HER2 targeted therapy**
- **Endocrine therapy**
 - Tamoxifen
 - Aromatase inhibitors (adjuvant)
 - Aromatase inhibitors (metastatic BC)
 - GnRHa and AI (metastatic BC)
 - Fulvestrant (metastatic BC)
- **Palliative chemotherapy as in women**

| | | |
|-----------|----------|------------|
| 2a | B | ++ |
| 5 | D | +* |
| 4 | D | ++ |
| 2b | B | ++ |
| 2b | B | - |
| 4 | C | +/- |
| 4 | C | +* |
| 4 | C | +/- |
| 4 | C | ++ |

***Participation in register study recommended**

Primary Inflammatory Breast Cancer (IBC, cT4d)

Oxford / AGO LOE / GR

- In case of invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d

++

- Staging

2c B ++

- Skin punch biopsy (at least 2; detection rate < 75%)

2c B +

- Preoperative chemotherapy

2c B ++

- Regimens as in non-inflammatory BC

- Anthracycline and taxane-based

2b B ++

- In HER2 + disease addition of trastuzumab

2b B ++

- Mastectomy after chemotherapy

2c B ++

- Breast conserving therapy in case of pCR

2b C +/-

- Sentinel excision only

3b C - -

- Radiotherapy

2c B ++

- Postoperative systemic therapy as in non-inflammatory BC

4 C ++

Axillary Metastasis in Carcinoma of Unknown Primary (CUP)

Oxford / AGO LOE / GR

| | | | |
|--|-----------|----------|------------|
| ➤ Mammography / Breast ultrasound | 3 | B | ++ |
| ➤ Breast MRI | 3 | B | ++ |
| ➤ Staging (CT thorax / abdomen, thyroid sonography, ENT investigation) | 3 | B | ++ |
| ➤ PET / PET-CT | 3b | B | +/- |
| ➤ Gene expression profiling (e.g. CupPrint™) | 2c | B | +/- |
| ➤ ER, PgR, HER2 | 5 | D | ++ |
| ➤ Axillary dissection | 3a | C | ++ |
| ➤ Systemic treatment according N+ tumor | 3a | C | ++ |
| ➤ Mastectomy if breast MRI is negative | 3a | C | - |
| ➤ Breast irradiation if breast MRI is negative | 3b | C | +/- |
| ➤ Irradiation of regional lymph nodes according to breast cancer guidelines | 3b | B | + |

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Paget's Disease of the Breast

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LOE / GR

- **Histological verification** ++
- **Mammography, sonography** 4 D ++
 - MR of the breast if other imaging negative 4 C +
- **Surgery must include NAC (R0)** 1c B ++
 - Wide excision (like DCIS) + radiotherapy 2b B +
 - Sentinel-node excision (SNE) 2b B +/-
- **Paget's disease with underlying disease (e.g. invasive breast cancer, DCIS)**
 - Therapy according to standard of the underlying disease 5 D ++
- **Isolated Paget's disease of the NAC (<5%):**
 - Surgical resection only, no adjuvant radiotherapy 4 D ++

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Malignant Phyllodes Tumor

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- **Complete (wide) local excision or MRM**
- **SNE / Axillary dissection in cN0**
- **Staging**
- **Systemic adjuvant therapy (chemo, endocrine)**
- **Adjuvant radiotherapy**
 - if T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)
- **Treatment of local recurrence**
 - R0 resection
 - Radiotherapy, chemotherapy after R1 resection
- **Distant metastases (very rare)**
 - Treatment like soft tissue sarcomas

**Oxford / AGO
LOE / GR**

| | | |
|-----------|----------|------------|
| 2b | B | ++ |
| 4 | C | -- |
| 5 | D | ++ |
| 4 | C | -- |
| 4 | C | -- |
| 2b | C | +/- |
| 4 | C | ++ |
| 4 | C | +/- |
| 4 | C | ++ |

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Sarcoma / Angiosarcoma of the Breast

(Note: very aggressive!)

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Treatment of Primary Disease:

- Mammography, Sonography to determine extent of disease
- Preoperative MRI to determine extent of disease
- Diagnosis by core biopsy
- Diagnosis by FNB
- Staging
- Prognostic factors: size, grade, margins
- Surgery with wide clear margins
 - Breast-conserving therapy if feasible
- Axillary dissection if cN0
- Adjuvant chemotherapy, radiotherapy
 - Adjuvant chemotherapy (anthracycline-based), radiotherapy in case of high risk (grade II-III, size > 5 cm, R1)

Oxford / AGO LOE / GR

| | | |
|----|---|-----|
| 3a | C | -- |
| 3a | C | ++ |
| 3a | C | ++ |
| 3a | C | -- |
| 4 | D | ++ |
| 3a | C | ++ |
| 3a | C | ++ |
| 3a | C | +/- |
| 3a | C | - |
| 3a | C | +/- |
| 4 | C | +/- |

Treatment of Local Recurrence:

- R0 resection
- Radiotherapy, chemotherapy after R1 resection

| | | |
|---|---|-----|
| 4 | C | ++ |
| 4 | C | +/- |

Distant Metastases / Unresectable Tumors:

- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)
- Antiangiogenic treatment
- Trabectedin (after anthracycline/ ifosfamide failure in leiomyosarcoma)

| | | |
|----|---|-----|
| 4 | C | ++ |
| 2b | B | + |
| 4 | C | +/- |
| 2b | B | + |

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Breast Cancer: Specific Situations (2/18)

Further information:

Update January 2014 – Fehm/Schneeweiss

Update January 2013 – Fersis/Friedrich

Update January 2012 – Lux/Lück

Update Februar 2011 – Janni/Huober

Update Januar 2010 – Mundhenke/Rody

Screened data bases: Pubmed 2000 – 2013, ASCO 2005 – 2013, SABCS 2005 – 2013, ECCO (2005 – 2013) n.d., EBCC (2005 – 2013) n.d., Cochrane data base (2012), n.d.

Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

Screened guidelines:

- NCCN: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

This chapter of rare diseases cannot deliver references for every statements separately but is providing them where possible.

No references

Breast cancer: Specific situations (3/18)

No further information

No references

Breast Cancer in Young Women ≤ 35 years (4/18)

Further information:

Breast cancer in young women is rare and probably a specific entity of high risk for recurrence. Therefore chemotherapy is almost always indicated. Radiotherapy seems to deliver additional benefit. Treatment with tamoxifen of up to ten years is beneficial.

It could be demonstrated that therapy induced amenorrhea might be of some benefit in premenopausal women but if this is especially true for pts < 35 years has not been proven.

Counselling for fertility protection should be offered and the patient needs to be informed about the possibility of compromised ovarian function due to adjuvant chemo- or endocrine therapy. In Germany the FERTIPROTECT Project is a platform to gain information how and where to get information.

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Prognosis in young women:

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Chemotherapy in young women:

1. Aebi S. Special issues related to the adjuvant therapy in very young women. Breast 2005, 14: 594-599 (Review)
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Benefit from trastuzumab:

1. Smith I, HERA study team: 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29-36
2. A.H. Partridge et al. The effect of age on breast cancer outcomes in women with her-2 positive breast cancer: results from the HERA trial J Clin Oncol 2013;44,2692–2698

Benefit from temporary amenorrhoea after adjuvant chemotherapy (chemotherapy induced or GnRHa-related)

1. M. Gnant et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360 (7) 679–691
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6. Yang B et al. Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials Breast 2013;22(2):150-7.

Surgery in young women (Surgery like ≥ 35 y - in particular BCT):

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Breast Cancer During Pregnancy or Breast Feeding (5/18)

Further information:

Screened data bases: Pubmed 2000 – 2013, ASCO 2005 – 2013, SABCS 2005 – 20013, Cochrane data base (n.d.)

Study link:

<http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft.html>

The individual breast cancer risk is strongly influenced by endocrine factors. Early menarche, late menopause, low number of children, short nursing periods, and increasing age at first birth are significant risk factors. The life style of the industrialized western world is thus causing an increase in breast cancer incidence.

Moreover, breast cancer incidence is also increasing with age. Pregnant breast cancer patients have an average age of about 32-38 years. Given the increasing average age of pregnant women, the co-incidence of a breast cancer diagnosis with the patient also being pregnant or nursing is becoming more frequent. This fact urgently needs to be acknowledged and accepted by physicians since the diagnosis of breast cancer is frequently being delayed in pregnancy. The average time interval between first symptoms and a definite diagnosis is about 5-15 months. Thus, the diagnosis is typically made at a later stage than outside of pregnancy. This delayed diagnosis is most likely one of the main reasons for the fact that overall survival of pregnant breast cancer patients is worse than that of non-pregnant breast cancer patients even though their stage-adapted prognosis is similar. As a consequence, we not only recommend that pregnant or nursing women need to examine their breast on a regular basis but also that clinical examination of breasts and loco-regional lymph nodes should be part of routine medical care during pregnancy and nursing period.

Another reason for the delayed diagnosis next to “simply not thinking about it” is the reluctance to order appropriate imaging and diagnostic test during pregnancy. Pregnancy or nursing period are no reason for delaying appropriate diagnostic work-up of a suspicious lesion. The same imaging techniques as in non-pregnant women are available. Breast ultrasound will not harm the fetus. Moreover, mammography can also be used if needed, since the danger of too much radiation for the fetus can be overcome by appropriate protective measures. MRI does not have the danger of radiation but

experiences with pregnant breast tissue is limited and interpretation may be difficult. Moreover, the position in the MRI may not be acceptable for most pregnant women. Thus, there is no reason to replace an indicated mammography by an MRI in pregnant patients. Physiological changes in pregnant or nursing breasts cause an increased false-positive rate in imaging procedures. Thus, in pregnant or nursing women, every suspicious palpable tumor definitely needs to be submitted to a histological diagnosis. As in non-pregnant patients, this can be done by minimal invasive techniques such as core or vacuum biopsies under local anesthesia. An open biopsy is only indicated in situations where minimal invasive procedures may not allow a definite diagnosis. In addition, pregnant women as well as their physicians may be more reluctant towards an open biopsy than towards a minimal invasive procedure, thus increasing again the danger of a delay in diagnosis. It is important to make the pathologist aware of the concurrent pregnancy or nursing period in order to avoid pregnancy-associated diagnostic histological changes to cause any diagnostic difficulties or even false-positive findings.

After diagnosis, therapy recommendations follow treatment outside of pregnancy with a few modifications: Therapeutic radiation of the breast is contraindicated during pregnancy so that a mastectomy would theoretically be the surgical method of choice. However, since adjuvant chemotherapy may be indicated in most cases anyway, the beginning of a radiation therapy may automatically be delayed by a few months thus allowing the pregnancy to reach (almost) full term by the end of chemotherapy. Thus, after delivery, radiation therapy is of course possible and thus breast conserving therapy is a valid option in breast cancer during pregnancy.

In general, chemotherapy can only be applied after the 12th week of pregnancy, i.e. after organogenesis. After the first trimester, chemotherapy does not cause an increased rate of malformations. Yet, there is an increased risk for growth retardation, premature labour, premature delivery, and intrauterine fetal death. Little is known about gonade development of and about the risk for malignancy in the children who were subjected to chemotherapy while still in utero. Indication for chemotherapy follows the guidelines for non-pregnant patients. Yet, one has to consider the individual teratogenic potential of the different chemotherapeutics and plan the delivery date accordingly. Among the most frequently used chemotherapeutics in breast cancer, antimetabolites such as methotrexate (or 5-fluorouracil) should not be used due to their teratogenic potential. For anthracyclines, there is no evidence for major complications. FEC, EC and Epi weekly are safe combinations. Undertreatment should be avoided. There is growing evidence that the use of taxanes is safe. So far, no major complications have been reported. The same is probably true for vinorelbine. Which is possible cytotoxic agent in pregnant metastatic breast cancer patients. Dose-dense chemotherapy does not appear to increase the risk of fetal or

maternal complications, but is not recommended at the moment. In conclusion, pregnancy is not a reason for withholding an indicated chemotherapy – the timing however, should take the delivery date into account.

Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot be recommended.

Results of studies of bisphosphonates in pregnant animals have shown maternal toxicity, fetal underdevelopment, embryoletality, hypocalcaemia and skeletal retardation, so that bisphosphonates are contraindicated in pregnancy.

The delivery should not be planned for the immediate three weeks following a chemotherapy cycle, since maternal side effects (e.g. fatigue, hematotoxicity) may increase the maternal risk for delivery-associated complications. Moreover, the placental excretion function disappears after delivery and the newborn may not be able to metabolize potential chemotherapy remainders.

Prognosis is not improved by cessation of nursing. However, nursing should be stopped before surgery in order to reduce volume of the breast and its blood flow. Moreover, nursing is not recommended during chemotherapy due to excretion of many chemotherapeutics into the milk.

There is neither evidence of direct damage to the fetus due to breast cancer nor of metastases into the fetus. Yet, rare placental metastases have been described.

Termination of pregnancy does not improve the prognosis of the breast cancer and thus is not considered a therapeutic option. Yet, depending on gestational age, termination may be considered if therapy options for the mother are severely compromised by the pregnancy.

Diagnosis of a malignancy during pregnancy causes extreme burden and conflicts for the pregnant women and their families touching on emotional, religious, social and ethical aspects next to medical issues. Most pregnant cancer patients want to “live long enough to see their child grow up”. Thus, decisions about continuing the pregnancy and about treatment should not only consider medical arguments but also take psychological as well as emotional needs of the pregnant patient into account.

References:

Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70

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Statement: Staging: ultrasound, chest X-ray if indicated:

7. Wang PI, et al. Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. AJR Am J Roentgenol 2012;198:785-792.

Statement: Surgery like in non-pregnant patients:

8. Annane K et al. Infiltrative breast cancer during pregnancy and conservative surgery. Fetal Diagn Ther 2005, 20: 442-444
9. Kuerer H et al., Conservative surgery and chemotherapy for breast carcinoma during pregnancy. Surgery 2002, 131: 108-110
10. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861

Statement: „Sentinel node biopsy“ during pregnancy:

11. Gentilini O et al., Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004, 15: 1348-1351
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Breast Cancer During Pregnancy (6/18)

No further information

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Statement: AC, FAC, (FEC):

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Statement: Taxanes:

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Statement Trastuzumab during pregnancy:

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29. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. Obstetrics and Gynecology 2005, 105: 642-643 (Case Report)

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Statement Bisphosphonate during pregnancy:

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Breast cancer during pregnancy (7/18)

Further information:

These statements are derived from common sense and literature cannot fully be assigned.

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In general:

1. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
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3. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70.

Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome:

4. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.

Statements: Delivery mode like in non-pregnant; Avoid delivery ≤ 3 weeks from prior chemotherapy:

5. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861

Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities:

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Pregnancy Associated Breast Cancer: Outcome (8/18)

Further information:

The outcome of pregnant breast cancer patients do not seem to be inferior to those being non pregnant. Data investigating this topic are inconsistent incorporating pregnant patients and PABC. A recent study however demonstrated a poorer survival for PABC. Most investigations did not report on the applied therapy which might be a confounding factor.

Pregnancy after breast cancer is safe and does not compromise the outcome. A healthy mother effect might be the reason, however, larger case series including also patients with advanced disease proposed additional effects.

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Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately:

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Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. *Breast*. 2003 Dec;12(6):516-21.
2. Kroman N, et al. Should women be advised against pregnancy after breast-cancer treatment? *Lancet*. 1997 Aug 2;350(9074):319-22.
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Geriatric Assessment (9/18)

Further information:

There is no accepted definition of the “older patient” but criteria exist for the assessment of biological age. The distinction between fit patients, vulnerable patients and frail patients has been established. Geriatric evaluation is an optimal tool for individually assessing the feasibility of treatment,

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Treatment for Fit Elderly Patients (10/18)

Further information:

Chemotherapy is feasible in fit elderly pts. The first randomized prospective trial in >600 pts. Demonstrated a survival benefit for patients treated with AC or CMF compared to those treated with Capecitabine alone. In an unplanned subset analysis, patients with hormone receptor negative disease derived the highest benefit from the combination therapy. Another German trial (ICE II) is investigating a combination of capecitabine with nab-paclitaxel compared to EC/CMF. In a retrospective analysis of four German randomized (neo)adjuvant trials taxanes seem feasible. Sequence therapies should be preferred; paclitaxel weekly seems to be the preferred taxane regimen in terms of toxicity for elderly pts. The study by Jones et al. evaluating TC as anthracycline free regimen showed especially good results in pts. older than 65 years.

In respect to older patients, current data increasingly suggest that the operation of the axilla could be avoided in cases of small tumours and a clinically negative axilla. Martelli et al. presented the update of a study including 671 patients ≥ 70 years (172 with axillary dissection and 499 patients without an operation of the axilla) at a median follow up time interval of 15 years. There was no significant difference in mortality within this group in the case of pT1 cN0 disease (10.7% versus 10.7%, $p=0.836$).

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8. Wildiers H: Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol.* 2007 Dec;8(12):1101-15
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Statement: Endocrine treatment (endocrine resp.):

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Statement: Chemotherapy in pts. < 70 years:

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Statement: Chemotherapy in pts. > 70 years:

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Statement: Radiotherapy:

Recently the long term results of a randomized phase 3 trial investigating the role of radiotherapy in elderly patients with breast conserving was reported. Patients 70 years or older with a clinically negative axilla, T1 tumors, breast conserving surgery, and hormone receptor positive tumor were randomized to Tamoxifen and radiation or to tamoxifen alone. Half of the pts were older than 75 years and around 60 % had no axillary surgery. Distant disease free survival and overall

survival at 10 years were without significant difference between the groups. Local relapse was rare however higher in the no radiation arm (Breast: 2% vs 9%; Axilla: 0 % vs 3%).

In a selected low risk population (T1, N0,) in elderly patients (< 70 years) with ER positive disease radiotherapy may be omitted when endocrine treatment with tamoxifen is planned.

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Statement: Trastuzumab:

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Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (11/18)

Further information:

Frailty is a factor that is crucial in modern times for assessing older patients who are fit to undergo more invasive/aggressive management. The presence of multiple co-morbidities also affects outcome of surgery and/or adjuvant treatment for older breast cancer patients and can increase the risk of death from causes other than breast cancer. There thus may be circumstances where non-operative therapies or even no treatment may be considered preferable due to these patients' factors and evaluations.

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Statement: Reduced standard treatment:

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Statement: No radiotherapy (≥ 70 y, pT1, pN0, Rec pos):

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Statement: Hypofractionated radiotherapy:

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Statement: No chemotherapy > 70 years and negative risk benefit analysis:

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Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (12/18)

Further information:

General:

The median age of male breast cancer is around 10 years later than in female. Survival seems to be not inferior to that of women with breast cancer. Male breast cancer patients developed secondary malignancies in more than 20% of the patients. In general the level of evidence is low and most recommendations are linked to those of postmenopausal women.

Diagnostic:

In men 80-90% of malignant breast tumors are not detected by mammography or they are covered by a gynecomastia. Ultrasound seems more effective

Surgery:

Wide excision in male breast cancer will almost always include resection of the nipple due to the small amount of breast tissue, and there is some evidence that this is not the most effective method of local control. To establish axillary status in clinically node-negative cases evidence is building up of the accuracy and low morbidity associated with sentinel-node biopsy in women. The technique has also been used in men with similarly encouraging results and sentinel node biopsy will probably become standard practice in the future for node-negative male breast cancer.

Genetic counselling:

Approximately 3-5% of female breast cancers are thought to result from autosomal dominant inheritance, particularly *BRCA1* and *BRCA2* mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in *BRCA2* than *BRCA1* families. In a southern Californian population, there were no *BRCA1* mutations in 54 patients with male breast cancer, whereas there was a *BRCA2* mutation in two (4%) patients. In 94 patients in the UK there were no germline *BRCA1* mutations, but five (6%) patients had *BRCA2* mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations within the *BRCA2* gene and risk of breast cancer.

Radiotherapy: Adjuvant radiotherapy has been delivered proportionally more frequently to men with breast cancer than to women, because the disease was more advanced locally in men and thought to be more aggressive. There is no evidence, however, that stage by stage the indications for radiotherapy should be different in men than in women. However,

retrospective studies that investigated the effects of radiotherapy in male breast cancer have not clearly shown a survival benefit.

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Statement: Diagnostic work up as in women

Statement: Mammography:

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5. Hines SL: The role of mammography in male patients with breast symptoms. Mayo Clin Proc. 2007 Mar;82(3):297-300

Statement: Ultrasound:

6. Caruso G: High-frequency ultrasound in the study of male breast palpable masses. Radiol Med (Torino). 2004 Sep;108(3):185-93

Statement: Standard-surgery: Mastectomy –men:

7. Shen. I et al Skin-sparing mastectomy: a survey based approach to defining standard of care. Am Surg. 2008 Oct;74(10):902-5
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Statement: Sentinel-node excision (SNE):

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Statement: Radiotherapy as in women (consider tumor breast relation!):

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Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer):

21. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26
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Statement: Screening for 2nd malignancies according guidelines:

25. Wernberg JA. Multiple primary tumors in men with breast cancer diagnoses: a SEER database review. *J Surg Oncol.* 2009 Jan 1;99(1):16-9

Statement: Systemic therapy:

22. Doyen J et al., *Ann Oncol.* 2009 Oct 27. [Epub ahead of print], Aromatase inhibition in male breast cancer patients: biological and clinical implications.
23. Eggemann H et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013;137(2):465-70.
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Male Breast Cancer: Systemic Therapy (13/18)

Further information:

Adjuvant chemotherapy: LoE: 4; References 1-4 (retrospective analysis, case series)

Adjuvant CMF chemotherapy was associated with an improvement in disease-free and overall survival. Only 50% of the patients (N=24) actually received the planned 12 cycles of CMF due to side effects.

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)

Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free survival and OS. Tamoxifen is well tolerated with the most common side effects being: Loss of libido (29%), weight gain (25%), heat flushes (21%), mood changes (21%), and depression (17%). The use of aromatase inhibitors has to be regarded as an experimental therapy at present. Due to the different physiological prerequisites for estrogen production in men and women, the effect of lowering serum estrogen levels in men has not yet been scientifically validated. Comparing adjuvant therapy with tamoxifen to aromatase inhibitors for 257 male breast cancer patients the overall survival was significantly better after treatment with tamoxifen.

Palliative endocrine therapy: LoE: 4; References 1-4 (retrospective analysis, case series)

In the metastatic setting there are data on achievement of stable disease being the maximum response to AI. Case reports do exist for anastrozol, letrozol and also fulvestrant.

Because of the low evidence level for the treatment of male breast cancer we believe that new studies should not exclude male patients. International registries should be participated in.

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Statement: Adjuvant Chemotherapy:

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15. Arriola E: Aromatase inhibitors and male breast cancer. *Clin Transl Oncol.* 2007 Mar;9(3):192-4
16. Eggemann H, Ignatov A, Smith BJ, Altmann U, von Minckwitz G, Röhl FW, Jahn M, Costa SD. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013 Jan;137(2):465-70.

17. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer *Breast Cancer Res Treat.* 2013;141(1):119-23
18. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer.* 2013;108(11):2259-63

Statement palliative chemotherapy:

19. Chitapanarux I: Gemcitabine plus cisplatin (GC): a salvage regimen for advanced breast cancer patients who have failed anthracycline and/or taxane therapy. *Gan To Kagaku Ryoho.* 2006 Jun;33(6):761-6

Inflammatory Breast Cancer (cT4d) (14/18)

Further information:

There is little information on inflammatory breast cancer (IBC) alone. Most retrospective analysis focus on T4 carcinomas without separating T4d cancer. Primary IBC is probably a distinct biological entity compared to non IBC.

Prospective randomised studies for the diagnosis and treatment of patients suffering from inflammatory breast cancer are still missing. The matter of current updates is aiming on the definition, including the confirmation of an invasive carcinoma as well as clinical signs of the skin affection $\geq 1/3$ of the breast involved (previous definition $> 2/3$ of the breast) [Dawood et al., 2011]. Biopsies of the skin should be acquired for diagnostic reasons [AGO 2c/B/+], with a detection rate of $< 75\%$.

Because of that a multidisciplinary approach consisting of preoperative chemotherapy, mastectomy and postoperative radiotherapy and adjuvant treatment is necessary. In the NOAH trial patients with locally advanced HER2 positive breast cancer were randomized to chemotherapy and trastuzumab preoperatively followed by adjuvant trastuzumab after surgery or to preoperative chemotherapy alone. 27% of the patients had inflammatory disease. pCR rates were significantly higher with the combination of trastuzumab and chemotherapy. In addition trastuzumab significantly improved event-free survival both in the whole study group and in pts with inflammatory breast cancer.

The use of Trastuzumab as neoadjuvant treatment option for inflammatory breast cancer [AGO 2b/B/++] is further supported by the current data of the NOAH-study [Semiglazov et al., 2011].

References:

Statement: Staging:

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Statement: Preoperative chemotherapy:

1. Ardavanis A: Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, and Fluorouracil chemotherapy, surgery, and radiotherapy: long-term results. Oncologist. 2006 Jun;11(6):563-73
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5. Van Laere et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct affymetrix gene expression datasets. Clin Cancer Res 2013;19:4685-96.

Statement: Regimens as in non-inflammatory BC:

6. Chia S et al. Locally advanced and inflammatory breast cancer J Clin Oncol 2008; 26: 786-790

Statement: in HER2 positive disease addition of trastuzumab:

7. Gianni L et al: Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomized controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375:377-384
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Statement: Mastectomy after chemotherapy:

12. Semiglazov V et al Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. Eur J Surg Oncol. 2011 Oct;37(10):856-63.
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17. Bristol IJ, Woodward WA, Strom EA, Cristofanilli M, Domain D, Singletary SE, Perkins GH, Oh JL, Yu TK, Terrefe W, Sahin AA, Hunt KK, Hortobagyi GN, Buchholz TA. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer Int J Radiat Oncol Biol Phys. 2008 Oct 1;72(2):474-84. Epub 2008 Apr 24
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Statement :Sentinel lymph node

1. Hidar S et al Sentinel lymph node biopsy after neoadjuvant chemotherapy in inflammatory breast cancer. Int J Surg. 2009 Jun;7(3):272-5. doi: 10.1016/j.ijsu.2009.04.012. Epub 2009 May 3.

Statement: Radiotherapy:

19. Chargari C, Kirova YM, Cottu P, Salmon RJ, Fourquet A Progressive inflammatory breast cancer in patient receiving chemotherapy: The importance of radiotherapy as a part of locoregional treatment. Radiother Oncol. 2009 Jan;90(1):160-1. Epub 2008 Sep 2

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Statement: Postoperative systemic therapy as in non-inflammatory BC

21. Veyret C: Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: ten-year results from the French Adjuvant Study Group GETIS 02 Trial. *Cancer*. 2006 Dec 1;107(11):2535-44
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Reviews:

23. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790
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Axillary Metastasis in Carcinoma of Unknown Primary (CUP) (15/18)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in $\leq 75\%$ of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management. Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial. (Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85) MRI is also reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour. (Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8) All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinalysis, fecal occult blood test. Jerusalem G: Ann Oncol 17 (Suppl 10) 2006:168-176) The appropriate treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal AH: Am J Surg. 2005 Oct;190(4):609-13) Probably these patients need to be treated as typical stage II patients. (Matsuoka, K: Breast Cancer. 2003;10(4):330-4 / Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005) The management of axillary node metastases in women with adenocarcinoma should be the same as the management of patients with lymph node metastases in breast cancer. If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed. (Buqat R: Bull Cancer. 2002 Oct;89(10):869-75).

The radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unknown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C/+/-]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% ($p < 0,001$) [Barton et al., 2011].

A systematic review of 24 retrospective studies enrolling 689 patients with axillary metastases of unknown origin showed that axillary CUP is associated with similar presentation, biology and outcome to node positive overt breast cancer and should be treated accordingly.

References:

1. Greco FA, Pavlidis N. Treatment for patients with unknown primary carcinoma and unfavorable prognostic factors. *Semin Oncol.* 2009;36:65–74

Statement: Mammography / Breast ultrasound/ Breast MRI:

1. Lalonde L: *Can Assoc Radiol J.* 2005 Dec;56(5):301-8
2. Ko EY: Breast MRI for evaluating patients with metastatic axillary lymph node and initially negative mammography and sonography. *Korean J Radiol.* 2007 Sep-Oct;8(5):382-9

Statement: Staging:

1. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. *Breast.* 2005 Apr;14(2):165-8
2. Jerusalem G: *Ann Oncol* 17 (Suppl 10) 2006: 168-176
3. Hemminki K, et al. Site-specific cancer deaths in cancer of unknown primary diagnosed with lymph node metastasis may reveal hidden primaries. *Int J Cancer* 2013; 132:944-50.

Statement: PET

4. Kwee Th.et al:This article Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis *Eur Radiol.* 2009 March; 19(3): 731–744.
5. Varadhachary GR: *Cancer.* 2004 May 1;100(9):1776-85
6. Pelosi E: *Q J Nucl Med Mol Imaging.* 2006 Mar;50(1):15-22.

Statement: Gene expression profiling:

1. Bender RA, Erlander MG. Molecular classification of unknown primary cancer. *Semin Oncol.* 2009;36:38–43.
2. Gauri et al., *JCO*, 26:4442-8, 2008;
3. Horlings et al., *JCO*, 26: 4435-4441, 2008
4. Pentheroudakis G, et al. Global microRNA profiling in favorable prognosis subgroups of cancer of unknown primary (CUP) demonstrates no significant expression differences with metastases of matched known primary tumors. *Clin Exp Metastasis* 2013; 30:431-9

Statement: ER, PR, HER2

1. Jue Wang et al Occult Breast Cancer Presenting as Metastatic Adenocarcinoma of Unknown Primary: Clinical Presentation, Immunohistochemistry, and Molecular Analysis Case Rep Oncol. 2012 Jan-Apr; 5(1): 9–16. F.
2. Anthony Greco et al Molecular Profiling in Unknown Primary Cancer: Accuracy of Tissue of Origin Prediction Oncologist. 2010 May; 15(5): 500–506.

Statement: Axillary dissection:

1. Bugat R: Bull Cancer. 2002 Oct;89(10):869-75
2. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. Breast. 2005 Apr;14(2):165-8
3. Pentheroudakis G et al. Axillary node metastases from carcinoma of unknown primary (CUPax): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119:1-11

Statement: Systemic treatment according N+ tumor:

1. Pentheroudakis G et al. Axillary node metastases from carcinoma of unknown primary (CUPax): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119:1-11
2. Pentheroudakis G, Greco FA, Pavlidis N. Molecular assignment of tissue of origin in cancer of unknown primary may not predict response to therapy or outcome: A systematic literature review. Cancer Treat Rev. 2009;35:221–227.
3. Matsuoka, K: Breast Cancer. 2003;10(4):330-4
4. Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005

Statement: Mastectomy without (in-)breast tumor:

LoE: 4; References 1-4 (retrospective analysis , case reports)

1. Khandelwal AH: Am J Surg. 2005 Oct;190(4):609-13
2. Matsuoka, K: Breast Cancer. 2003;10(4):330-4
3. Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005)
4. Bugat R: Bull Cancer. 2002 Oct;89(10):869-75

Statement: Breast irradiation if breast MRI is negative:

1. Bugat R: Bull Cancer. 2002 Oct;89(10):869-75
2. Barton SR, Smith IE, Kirby AM, Ashley S, Walsh G, Parton M. The role of ipsilateral breast radiotherapy in management of occult primary breast cancer presenting as axillary lymphadenopathy. Eur J Cancer. 2011;47(14):2099-106.

Paget's Disease of the Breast (16/18)

Further information:

Paget's disease is a rare disease, therefore separate literature is scarce.

References:

Statement: MR of the breast if other imaging negative

1. Moon JY, et al. Malignant invasion of the nipple-areolar complex of the breast: usefulness of breast MRI. Am J Roentgenol. 2013; 201:448-55.

Statement: Wide excision (like DCIS) + radiotherapy:

1. Bijker N: EORTC Breast Cancer Cooperative Group. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer. 2001 Feb 1;91(3):472-7.
2. Marshall JK: Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. Cancer. 2003 May 1;97(9):2142-9

Statement: Sentinel-node excision (SNE):

3. Bijker N: EORTC Breast Cancer Cooperative Group. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. Cancer. 2001 Feb 1;91(3):472-7.

Statement: Paget's disease with underlying disease (e.g. invasive breast cancer, DCIS): therapy according to standard of the underlying disease:

4. M. Caliskan et.al (2008) Paget disease of the breast: experience of the Europ. Inst. of Oncol and review of the Literature: Breast Can. Res. Treat. 112: 513-521

Statement: Isolated Paget's disease of the NAC (<5%): surgical resection only, no adjuvant radiotherapy

Malignant Phyllodes Tumor (17/18)

Further information:

Phyllodes tumors (PTs) of the breast are biphasic neoplasms composed of epithelium and a spindle-cell stroma. Currently, PTs are classified as benign, borderline, or malignant based on histopathologic features. The presence of pain ($P = 0.03$), tumor size > 5 cm ($P = 0.005$), postmenopausal status ($P < 0.04$), heavy cellular pleomorphism ($P = 0.007$), high mitotic activity ($P = 0.002$), tumoral grade ($P = 0.006$) and metastasis ($P < 0.00001$) were prognostic factors of poor survival. (Roa JC: Pathol Int. 2006 Jun;56(6):309 / Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11).

However, histologic classification does not always predict outcome. Stromal c-Kit positivity and epithelial endothelin 1 negativity are more often associated with malignant PTs; however, only positive margin status is significantly associated with tumor behavior (Esposito NN: Arch Pathol Lab Med. 2006 Oct;130(10):1516-21).

Mastectomy was not found to provide a benefit in PT-specific survival compared with wide excision in malignant phyllodes tumor of the breast. Women undergoing wide excision had at the minimum similar cancer-specific mortality compared with those who received mastectomy. (Macdonald OK: Cancer. 2006 Nov 1;107(9):2127-33 / Fou A: Am J Surg. 2006 Oct;192(4):492-5 / Cheng SP: World J Surg. 2006 Aug;30(8):1414-21). Some authors have seen an improved survival after Mastectomy (Ben Hassouna J: Am J Surg. 2006 Aug;192(2):141-7). An axillary lymph node dissection is not indicated (Granic M: Acta Chir Jugosl. 2006;53(1):57).

The treatment of local recurrent disease remains unsuccessful in most malignant phyllodes tumor patients. (Soumarova R: Arch Gynecol Obstet. 2004 May;269(4):278-81). Surgery for locally recurrent tumours should aim to achieve adequate surgical margins (Tan EY: ANZ J Surg. 2006 Jun;76(6):476-80). The role of chemotherapy, radiotherapy, and hormonal manipulation in both the adjuvant and palliative settings remain to be defined (Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11 / Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94 / Parker SJ: Postgrad Med J. 2001 Jul;77(909):428-35).

References:

Statement: Complete (wide) local excision or MRM (LoE: 2c):

References 1-4 (retrospective analysis , case reports)

1. Macdonald OK: Cancer. 2006 Nov 1;107(9):2127-33
2. Fou A: Am J Surg. 2006 Oct;192(4):492-5
3. Cheng SP: World J Surg. 2006 Aug;30(8):1414-21
4. Ben Hassouna J: Am J Surg. 2006 Aug;192(2):141-7
5. Pezner et al Malig. Phy. Tu. Of the breast: local control rates with surgery alone (2008): Int. J Radiat. Oncol. Biol. Phys
6. Mituš JW, et al. Changes in the clinical characteristics, treatment options, and therapy outcomes in patients with phyllodes tumor of the breast during 55 years of experience. Med Sci Monit 2013; 19:1183-7.
7. Mishra SP, et al. Phyllodes tumor of breast: a review article. ISRN Surg. 2013;2013:361469.

Statement: SNE / Axillary dissection in cN0 (LoE: 4):

References 1-3 (retrospective analysis, case reports)

1. Granic M: Acta Chir Jugosl. 2006;53(1):57
2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94
3. Malard Y: J Gynecol Obstet Biol Reprod (Paris). 2004 Nov;33(7):589-99

Statement: Staging:

4. Hollingsworth AB, Stough RG, O'Dell CA, Brekke CE. Breast magnetic resonance imaging for preoperative locoregional staging Am J Surg. 2008 Sep;196(3):389-97

Statement: Systemic adjuvant therapy/ Chemotherapy (LoE: 4):

References 1 (cohort studies , case reports)

1. Morales-Vásquez F: Adjuvant chemotherapy with doxorubicin and dacarbazine has no effect in recurrence-free survival of malignant phyllodes tumors of the breast. Breast J. 2007 Nov-Dec;13(6):551-6
2. Spitaleri G, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol. 2013; 88:427-36.

Endocrine therapy (LoE: 5):

1. Spitaleri G, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol. 2013; 88:427-36.

Statement: Adjuvant radiotherapy: Radiotherapy after R0 (LoE: 4):

References 1-3 (retrospective analysis, cohort studies)

1. Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11
2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94
3. Parker SJ: Postgrad Med J. 2001 Jul;77(909):428-35
4. Belkacemi Y. et al. Phylloides. Tumor. Of the breast (2007): Int. J. Radiat. Oncol. Biol. Phys.
5. Spitaleri G, et al. Breast phyllodes tumor: a review of literature and a single center retrospective series analysis. Crit Rev Oncol Hematol. 2013; 88:427-36.

Statement: Adjuvant radiotherapy, if $T \geq 2\text{cm}$ (BCT) or $T \geq 10\text{cm}$ (mastectomy):

6. Pezner et al Malig. Phy. Tu. Of the breast: local control rates with surgery alone (2008): Int. J Radiat. Oncol. Biol. Phys

Statement: Treatment of local recurrence => R0 Resection: LoE: 4; References (retrospective analysis , case reports):

1. Soumarova R: Arch Gynecol Obstet. 2004 May;269(4):278-81
2. Tan EY: ANZ J Surg. 2006 Jun;76(6):476-80).

Statement: Radiotherapy, chemotherapy after R1 resection

Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas

1. Jardim DL, et al. Comprehensive characterization of malignant phyllodes tumor by whole genomic and proteomic analysis: biological implications for targeted therapy opportunities. Orphanet J Rare Dis 2013; 8:112.

Sarcoma / Angiosarcoma of the Breast (18/18)

Further information:

The management of angiosarcomas at different sites were recently summarized in review. Radical surgery with complete RO resection is the primary treatment of choice. Because of the high risk of local recurrence radiotherapy should be considered. In view of the risk of metastatic disease there is a rationale for adjuvant chemotherapy. However up to now there is no convincing evidence to support the use of adjuvant chemotherapy. Active agents in metastatic angiosarcoma are anthracyclines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

Reference:

Young RJ et al:Angiosarcoma:Lancet Oncol 2010;11:983-991

Primary angiosarcoma (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent.

Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm. The imaging features of AS are non-specific in mammography and up to 33% are undetectable. On ultrasound examination, there is a heterogenous echogenicity with hyperechoic areas without acoustic shadowing. The most useful imaging technique to determine the extent of AS is breast MRI that shows hypervascular, heterogenous masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images.

Histologic grading is important for the assessment of prognosis with the 5-year recurrence free survival of 76% for low grade AS and 15% for high grade AS but reported survival data differ widely. The role of adjuvant radiotherapy and

chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with anthracycline-ifosfamide or gencitabine-taxane. Four had complete response and 10 a partial response (48% overall response rate), but there was no difference in DFS or OS between patients who received no adjuvant treatment. In an older series, 20% of low, 40% of intermediate and 71% of high-grade lesions recurred following chemotherapy. In contrast 27%, 40% and 100% of low, intermediate and high-grade lesions recurred in patients who did not receive adjuvant chemotherapy. Therefore, the role of adjuvant chemotherapy for AS of the breast remains unclear.

Secondary angiosarcoma (AS) occurs following radiotherapy after breast conserving therapy or after chest wall irradiation after mastectomy. Therefore the term radiotherapy-associated angiosarcoma may also be used. Another, much rarer occurrence of post-treatment angiosarcoma is in the upper limb following longstanding lymphoedema after mastectomy, with or without radiotherapy. This has also been called Steward-Treves syndrome and is not radiotherapy-associated and therefore not considered here.

The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation.

Current data show that not the type of operation in the case of sarcomas of the breast, particularly the angiosarcoma, a serious disease that could appear 10-15 years after radiation therapy, but factors such as size, grading and especially the adequate safety margins are important diagnostic factors. Thus, breast conserving surgeries could be performed with larger safety margins, if feasible and after given consent of the associated risk [AGO 4/C/++] (Al-Benna et al. 2010; Voutsadakis et al., 2011). It should be diagnosed through punch biopsy not via fine-needle biopsy. Postoperatively an anthracycline-based chemotherapy in combination with radiotherapy could be considered particularly in high-risk situations [AGO 4/C/+-] (Barrow et al., 1999). If metastases have already occurred, paclitaxel as well as liposomal doxorubicin should be applied especially in patients with angiosarcoma. In case of unsuccessful treatment with anthracycline and ifosfamid, trabectedin could be used in patients suffering from leiomyosarcoma [AGO 2b/B/+] (Schöffski et al., 2011).

References:

1. Donnell RM, Rosen PP, Liebermann PH et al. Angiosarcoma and other vascular tumours of the breast. Pathologic analysis as a guide to prognosis. Am Surg Pathol 1981; 5: 629-642
2. Rosen P, Kimmel M, Ernsberger D. Mammary angiosarcoma. The prognostic significance of tumor differentiation. Cancer 1988; 62: 2145-2151

3. Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MK. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. *Br J Cancer*. 1995;72(2):469-75.
4. Strobbe LJ, Peterse HL, van Tinteren H. Angiosarcoma of the breast after conservation therapy for invasive cancer. The incidence and outcome. *Breast Cancer Res Treat* 1998; 47: 101-109.
5. Barrow BJ, Janjan NA, Gutman H, Benjamin RS, Allen P, Romsdahl MM, Ross MI, Pollock RE. Role of radiotherapy in sarcoma of the breast- a retrospective review of the M.D. Anderson experience. *Radiother Oncol*. 1999;52(2):173-8
6. Rosen PP. *Rosen's breast pathology*. Philadelphia: Lippincott Williams & Wilkins 2001.
7. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. *Cancer* 2001; 92: 172-180
8. Vorburger S, Xing Y, Hunt K et al. Angiosarcoma of the breast. *Cancer* 2005; 104: 2682-2688.
9. Sher T, Hennessy BT, Valero V et al. Primary angiosarcomas of the breast *Cancer* 2007; 110; 173-178
10. Yang WT, Hennessy BT, Dryden MJ, et al. Mammary angiosarcoma imaging findings in 24 patients. *Radiology* 2007; 242:725-734
11. Sher T, Hennessy BT, Valero V, Broglio K, Woodward WA, Trent J, Hunt KK, Hortobagyi GN, Gonzalez-Angulo AM. Primary angiosarcomas of the breast. *Cancer*. 2007;110(1):173-8.
12. Penel N (2008) Ph II weekly Paclitaxel for unresectable angiosarcoma: ANGIOTAX-study: *J. Clin Oncol*. 26: 5269-5274
13. Lum YW, Jacobs L. Primary breast sarcoma. *Surg Clin North Am*. 2008;88(3):559-70, vi.
14. Glazebrook K.N. (2008) Angiosarcoma of the breast, *AJR, Woman Imaging*
15. [No authors listed]: *Drugs R D*. 2006;7(5):317-28. Links
16. Trabectedin: Ecteinascidin 743, Ecteinascidin-743, ET 743, ET-743, NSC 684766. YondelisTM
17. Al-Benna S, Poggemann K, Steinau HU, Steinstraesser L. Diagnosis and management of primary breast sarcoma. *Breast Cancer Res Treat*. 2010;122(3):619-26
18. Schöffski P, Taron M, Jimeno J, Grosso F, Sanfilipio R, Casali PG, Le Cesne A, Jones RL, Blay JY, Poveda A, Maki RG, Nieto A, Tercero JC, Rosell R. Predictive impact of DNA repair functionality on clinical outcome of advanced sarcoma patients treated with trabectedin: a retrospective multicentric study. *Eur J Cancer*. 2011;47(7):1006-12
19. Voutsadakis IA, Zaman K, Leyvraz S. Breast sarcomas: current and future perspectives. *Breast*. 2011;20(3):199-204

20. Kaklamanos IG, Birbas K, Syrigos KN, Vlachodimitropoulos D, Goutas N, Bonatsos G. Breast angiosarcoma that is not related to radiation exposure: a comprehensive review of the literature. *Surg Today*. 2011;41(2):163-8
21. Sheth GR, Cranmer LD, Smith BD, Grasso-Lebeau L, Lang JE. Radiation-induced sarcoma of the breast: a systematic review. *Oncologist*. 2012;17(3):405-18.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Follow-Up

Breast Cancer Follow-Up

- **Versions 2002–2013:**
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Breast Cancer Follow-Up Objectives

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- **Improve quality of life**
- **Improve physical performance**
- **Reduce therapy related side effects
(after surgery, systemic therapy and
radiation therapy)**

**Oxford / AGO
LoE / GR**

2b B +

2b B +

2b B +

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Breast Cancer Follow-Up Objectives

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➤ Re-evaluation of current adjuvant therapy

5 D ++

- incl. monitoring of compliance with endocrine therapies

➤ Pro-active improvement of compliance:

++

- Patient information about efficacy data of 5-10 year endocrine therapy
- Early therapy of side effects (sports, NSAIDs, vitamin D/Calcium)

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Early detection of curable events

- In-breast recurrence
- Loco-regional recurrence

1a B ++

1a B ++

Early detection of metastases

- Early detection of symptomatic metastases
- Early detection of asymptomatic metastases

3b C +

1a A -

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➤ **Psycho-social aspects of support and counseling**

4 C +

- **Pregnancy, contraception, sexuality, quality of life, menopausal symptoms, fear for recurrence**

➤ **Second opinion on primary therapy**

2c B ++

➤ **General counseling (genetics, HRT)**

2c C +

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Breast Cancer Follow-Up Objectives

**Intervention with regard to co-morbidities and life-style risks
in order to reduce negative effects on disease course**

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- **Treatment of type II-diabetes** ++
(>25% undetected DM in postmenopausal BC patients)
- **Weight intervention** 2a B +
(if BMI <18.5 and >40)
- **Smoking** 2b B ++
(bc related mortality 2 x and BC unrelated mortality 4 x elevated)
- **Moderate sport intervention when physical activity was reduced** 1b A ++
(rel. reduction of mortality up to 25%)

Follow-up Objectives Reported by Patients

Oxford LoE 4 C

- **Examination of the breast**
- **Reassurance**
- **Guidance of patients, answering questions**
- **Evaluation of treatment and treatment of side effects**
- **Psychosocial support**

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Follow-up Goals Reported by Health Professionals and Patients

| | Health professionals | Patients |
|------------------------|--|--|
| Often mentioned | Early detection of recurrences and second tumors | Examination of the breast |
| | Psychosocial support | Reassurance |
| | Guidance, information and referral | Guidance of patients, answering questions |
| Occasionally mentioned | Evaluation of treatment and treatment side effects | Evaluation of treatment and treatment side effects |
| | Early detection of metastases | Psychosocial support |
| | Clinical trials, building own database | |

Routine Follow-Up Examinations in Asymptomatic Patients

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Tests:

- History (specific symptoms)
- Physical examination
- Breast self-examination
- Mammography
- Sonography of the breast
- Routine MRI of the breast
- MRI of the breast in case of inconclusive conventional imaging
- Pelvic examination

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1a A ++

1a B ++

5 D +

1a A ++

2a B ++

3b B +/-

3b B +

5 D ++

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| | Oxford / AGO LoE / GR | | |
|---|--------------------------|---|---|
| ➤ Routine biochemistry (incl. tumor markers) | 1a | A | - |
| ➤ Ultrasound of the liver | 1a | A | - |
| ➤ Bone scan | 1a | A | - |
| ➤ Chest X-ray | 1a | A | - |
| ➤ CT of chest, abdomen and pelvis | 2a | D | - |
| ➤ Detection of isolated / circulating tumor cells | 2a | D | - |
| ➤ PET | 2b | B | - |
| ➤ Whole body MRI | 2b | B | - |

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Early Detection of Potentially Curable Events

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Local recurrence & in-breast recurrence:

- Incidence 7–20%
(depending on time of F/U)
- Breast self-examination
- Physical examination, mammography & US
- Magnetic resonance imaging (MRI)

| | | |
|----|---|-----|
| 5 | D | + |
| 1a | B | ++ |
| 3b | B | +/- |

Early Detection of Potentially Curable Events

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Contralateral breast cancer:

- Rel. risk: 2,5–5
- Incidence: 0,5–1,0 % / year
- **Breast self-examination**
- **Physical examination, mammography & US**
- **Routine breast MRI**

| | | |
|-----------|----------|-----------|
| 5 | D | + |
| 1a | A | ++ |
| 5 | D | - |

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Early Detection of Potentially Curable Events

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Unrelated site carcinoma:

- Colon RR 3,0; endometrium RR 1,6
ovary RR ca. 1,5
- Screening for secondary malignancies
according to current guidelines ++
- Pelvic examination and PAP smear 5 D ++
- Routine endometrial ultrasound / biopsy 1b B -

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Follow-Up Care for Breast Cancer (incl. LCIS/DCIS)

Recommendations for asymptomatic pts.

(modified ASCO guidelines 2012, NCCN 2.2011 and S3 national German guideline 2012)

| Clinical follow-up | | Follow-Up* | | | | Screening | |
|---|---------------------|--|---|---|--------------------------------|-----------|-------------------------------|
| Years after primary therapy | | 1 | 2 | 3 | 4 | 5 | > 6 |
| History, physical examination, counseling | | inv.: every 3 months | | | inv.: every 6 months | | inv.: every 12 months |
| | | LCIS / DCIS: every 6-12 months | | | | | LCIS/DCIS: every 12 months |
| Self-examination | | monthly | | | | | |
| Imaging modalities and biochemistry | | indicated only by complaints, clinical findings or suspicion of recurrence | | | | | |
| Mammo- graphy and sono- graphy | inv.: BCT** | ipsilat.: every 6-12 months contralat.: every 12 months | | | on both sides: every 12 months | | |
| | inv.: Mastectomy | contralateral every 12 months | | | | | |
| | LCIS / DCIS | every 12 months | | | | | |

* Continued follow-up visits if still on adjuvant treatment

** First mammography 6-12 months after completion of breast-conserving radiotherapy

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Breast Cancer Follow-up Duration. Breast Nurses.

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➤ Duration of follow-up

➤ until 5 yrs

1c A ++

➤ until 10 yrs

1c A +

➤ Surveillance by specialized breast nurses

2b B +/-*

***Studies recommended**

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Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients

- **Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.**
- **ER-positive patients have stable risk over many years requiring long term surveillance.**
- **However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.**

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Version 2014.1

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Further
Information

References

Breast Cancer Follow-Up (2/17)

Further information:

Update 08. Januar 2009 – Janni / Gerber

Update 14. Januar 2010 – Diel / Kaufmann : no changes

Update Januar 2011 – Lux/Scharl: minor changes and additions

Update Januar 2012 – Kümmel/Bauerfeind: some changes and additions

Update Januar 2013 – Möbus Mundhenke: some changes and additions

Update Januar 2014 – Solomayer, Thomssen: some changes and additions

Screened data bases: Pubmed 1998 - 2014.

Screened guidelines:

- Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

Goldhirsch A, Wood WC, Coates AS et al.: Ann Oncol. 2011 Aug;22(8):1736-47.

- CMA: <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

- NCCN 2.2011: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

- Cochrane Collaboration: http://www.cochrane.org/reviews/en/topics/52_reviews.html

No references

Breast Cancer Follow-Up Objectives (3/17)

Further information:

There are indications, that physical activity (as for example walking, yoga, ...) and weight reduction during follow-up is able to improve quality of life, improve physical performance, reduce Fatigue, and optimize Outcome. Therefore during follow-up patients should be encouraged to and be supported in measures to achieve these goals.

References:

Statement: Obesity, physical activity and quality of life

1. Vaskuil et al. Maintenance of physical activity and body weight in relation to subsequent quality of life in postmenopausal breast cancer patients. *Annals of Oncology* 21: 2094–2101, 2010.
2. NCCN-Guidelines Version 1.2011. Cancer-related Fatigue.
3. Can yoga improve fatigue in breast cancer patients? A systematic review. Cramer H, Lange S, Klose P, Paul A, Dobos G: *Acta Oncol.* 2011 Dec 5.
4. Carson JW, Carson KM, Porter LS et al. (2009): Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. *Support Care Cancer*, 17: 1301-1309.
5. Bower JE, Garet D, Sternlieb B et al.: Yoga for persistent fatigue in breast cancer survivors: A randomized controlled trial. *Cancer*. 2011 Dec 16.
6. Bicego D, Brown K (2009): Effects of Exercise on Quality of Life in Women Living with Breast Cancer: A Systematic Review. *The Breast Journal*, 15,1: 45-51.
7. Cramp F, Daniel J. (2008): Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*, Issue 2.

Statement: Obesity and breast cancer prognosis

1. Ewertz M, Jensen MB, Gunnarsdóttir KÁ, Højris I, Jakobsen EH, Nielsen D, Stenbygaard LE, Tange UB, Cold S. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol.* 29(1):25-31, 2011

Breast Cancer Follow-Up Objectives (4/17)

Further information:

Based on the variety of adjuvant treatment options and emerging new evidence within short time, patients' current and ongoing adjuvant therapy should be re-evaluated repeatedly in order to assure state of the art treatment.

With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. However, the benefit of this ongoing counselling has to be substantiated yet.

During follow-up compliance with endocrine therapies should be monitored. Predictors for discontinuation of treatment are young age and old age, BCT (vs mastectomy), more than 2 comorbidities, higher co-payment required, smaller blister pack, and prescription by general practitioner.

Predictors for good compliance are marriage, adjuvant chemotherapy, adjuvant radiotherapy.

Intensified surveillance has proved to decrease the lead time until the detection of distant metastases in comparison to conventional surveillance, but has not shown to improve overall survival. In the context of novel treatment modalities for distant disease, however, this objective should be re-examined.

References:

Statement: Re-evaluation of current adjuvant therapy

1. Expert opinion Organkommission

Statement: Monitoring of compliance

1. Hershman DL et al., SABCS, 2010
2. Hershman DL et al. Early Discontinuation and Nonadherence to Adjuvant Hormonal Therapy in a Cohort of 8,769 Early-Stage Breast Cancer Patients. J Clin Oncol 28:4120-4128
3. Neven P, Markopoulos C, Tanner MME et al.: The Impact of Educational Materials on Compliance and Persistence with Adjuvant Aromatase Inhibitors: 2 Year Follow-Up and Final Results from the CARIATIDE Study. SABCS 2011 [P5-16-02].
4. Lueck H-J, Hadji P, Harbeck N et al.: 24 Months Follow-Up Results from PACT (Patient's Anastrozole Compliance to Therapy Programme), a Non-Interventional Study Evaluating the Influence of a Standardized Information Service on Compliance in Postmenopausal Women with Early Breast Cancer. SABCS 2011 [P5-17-05].

Statement: Early Detection of Distant Disease

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 271: 1593–1597
3. Rojas,MP et al: Follow-up strategies for women treated for early breast cancer. Review. The Cochrane Library 4 (2004) 1-16.
4. The GIVIO Investigators (1994) Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 271: 1587–1592

Breast Cancer Follow-Up Objectives (5/17)

Further information:

The main objective of following patients after the primary treatment of breast cancer is the detection of potentially curable events, particularly the detection of local recurrences and contralateral breast cancer. With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. The psycho-social aspects of support and counselling will gain relevance as more patients survive breast cancer and will encounter long-term treatment.

References:

Statement: Early Detection

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Cohen I, Beyth Y, Tepper R The role of ultrasound in the detection of endometrial pathologies in asymptomatic postmenopausal breast cancer patients with tamoxifen treatment. Obstet Gynecol Surv 1998 Jul;53(7):429-38
3. De Bock GH, Bonnema J, van Der Hage J, Kievit J, van de Velde CJH: Effectiveness of Routine Visits and Routine Tests in Detecting Isolated Locoregional Recurrences After Treatment for Early-Stage Invasive Breast Cancer: A Meta-Analysis and Systematic Review. Journal of Clinical Oncology 2004 Vol 22, No 19 (October 1): 4010-4018
4. Drew PJ, Kerin MJ, Turnbull LW, Imrie M, Carleton PJ, Fox JN, Monson JR. Routine screening for local recurrence following breast-conserving therapy for cancer with dynamic contrast-enhanced magnetic resonance imaging of the breast. Ann Surg Oncol 1998 Apr-May;5(3):265-70
5. Follow-up after treatment for breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998; 158 Suppl 3: S65 - 70
6. Giorda G, Crivellari D, Veronesi A, Perin T, Campagnutta E, Carbone A, Scarabelli C. Comparison of ultrasonography, hysteroscopy, and biopsy in the diagnosis of endometrial lesions in postmenopausal tamoxifen-treated patients. Acta Obstet Gynecol Scand 2002 Oct;81(10):975-80
7. E. Grunfeld, D. Mant, P. Yudkin et al. Routine follow up of breast cancer in primary care: randomised trial BMJ 1996;313:665-669 (14 September)

Statement: Psycho-social aspects

1. Fors EA, Bertheussen GF, Thune I et al.: Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psycho-Oncology* 2011; 20: 909-918.
2. Davies JE, French MA, Allen T. Follow-up for a fearful patient. *Adv Nurse Pract* 2001 Feb;9(2):22
3. Drolet M, Maunsell, Brisson, Brisson C, Mâsse B, Deschênes L. Not Working 3 Years After Breast Cancer: Predictors in a Population-Based Study. *JCO*, Vol 23, No 33 (November 20), 2005:8305-8312
4. Maunsell E, Brisson J, Deschenes L. Social support and survival among women with breast cancer. *Cancer* 1995 Aug 15;76(4):631-7
5. ScheierMF, Helgeson VS, Schulz R, Colvin S, Berga S, Bridges MW, Knapp J, Gerszten K, Pappert WS. Interventions to Enhance Physical and Psychological Functioning Among Younger Women Who Are Ending Nonhormonal Adjuvant Treatment for Early-Stage Breast Cancer *JCO*, Vol 23, No 19 (July 1), 2005: pp. 4298-4311

Breast Cancer Follow-Up Objectives (6/17)

Further information:

The main objective of following patients after the primary treatment of breast cancer is the detection of potentially curable events, particularly the detection of local recurrences and contralateral breast cancer. With increasing complexity and time length of primary adjuvant treatment, the surveillance and counselling during the follow-up period becomes increasingly important. The psycho-social aspects of support and counselling will gain relevance as more patients survive breast cancer and will encounter long-term treatment.

References:

Statement: Early Detection

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Cohen I, Beyth Y, Tepper R The role of ultrasound in the detection of endometrial pathologies in asymptomatic postmenopausal breast cancer patients with tamoxifen treatment. Obstet Gynecol Surv 1998 Jul;53(7):429-38
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5. Follow-up after treatment for breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998; 158 Suppl 3: S65 - 70
6. Giorda G, Crivellari D, Veronesi A, Perin T, Campagnutta E, Carbone A, Scarabelli C. Comparison of ultrasonography, hysteroscopy, and biopsy in the diagnosis of endometrial lesions in postmenopausal tamoxifen-treated patients. Acta Obstet Gynecol Scand 2002 Oct;81(10):975-80
7. E. Grunfeld, D. Mant, P. Yudkin et al. Routine follow up of breast cancer in primary care: randomised trial BMJ 1996;313:665-669 (14 September)

Statement: Psycho-social aspects

1. Fors EA, Bertheussen GF, Thune I et al.: Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psycho-Oncology* 2011; 20: 909-918.
2. Davies JE, French MA, Allen T. Follow-up for a fearful patient. *Adv Nurse Pract* 2001 Feb;9(2):22
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Breast Cancer Follow-Up Objectives (7/17)

Further information:

Intervention in order to treat co-morbidities and to counsel for life-style risks is recommended aimed at reducing unfavourable effects on the course of the breast cancer disease.

Treatment of type II-diabetes

./.

Weight intervention

Véronique Chajès, Isabelle Romieu. Nutrition and breast cancer. Maturitas, Volume 77, Issue 1, January 2014, Pages 7–11

Smoking

./.

Moderate sport intervention when physical activity was reduced

Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013 Aug;22 Suppl 2:S30-7.

Follow-up objectives reported by patients (8/17)

Further information:

Expectations of follow-up and objectives are differently reported by health professionals and patients.

Reference:

Kwast AB, Drossaert CH, Siesling S; follow-up working group. Breast cancer follow-up: from the perspective of health professionals and patients. Eur J Cancer Care (Engl). 2013 Nov;22(6):754-64. doi: 10.1111/ecc.12094. Epub 2013 Jul 8.

Follow-up Goals Reported by Health Professionals and Patients (9/17)

No further information

Reference:

Kwast AB, Drossaert CH, Siesling S; follow-up working group. Breast cancer follow-up: from the perspective of health professionals and patients. Eur J Cancer Care (Engl). 2013 Nov;22(6):754-64. doi: 10.1111/ecc.12094. Epub 2013 Jul 8.

Routine Follow-Up Examinations in Asymptomatic Patients (10/17)

Further information:

Routine follow-up examinations in asymptomatic patients should comprise history (for specific symptoms), physical examination, Mammography, sonography of the breast, MRI of the breast in case of inconclusive conventional imaging and pelvic examination. Breast self-examination is encouraged by expert especially for self awareness, but no survival benefit has been scientifically substantiated so far. Additional examination (compare following slide) are explicitly discouraged for the time being.

References:

Statement: History (specific symptoms)

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Follow-up after treatment for breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998; 158 Suppl 3: S65 - 70

Statement: Physical examination

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Follow-up after treatment for breast cancer. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Can Med Assoc J 1998; 158 Suppl 3: S65 - 70

Statement: Breast self-examination

Expert Opinion

Statement: Mammography

1. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, Halberg F, Somerfield MR, Davidson NE; American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. De Bock GH, Bonnema J, van Der Hage J, Kievit J, van de Velde CJH: Effectiveness of Routine Visits and Routine Tests in Detecting Isolated Locoregional Recurrences After Treatment for Early-Stage Invasive Breast Cancer: A Meta-Analysis and Systematic Review. Journal of Clinical Oncology 2004 Vol 22, No 19 (October 1): 4010-4018
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Statement: Sonography of the breast

1. Dillon MF, Hill AD, Quinn CM, O'Doherty A, McDermott EW, O'Higgins N. The accuracy of ultrasound, stereotactic, and clinical core biopsies in the diagnosis of breast cancer, with an analysis of false-negative cases. Ann Surg. 2005 Nov;242(5):701-7.
2. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, Mallek R, Sickles EA. Follow-up of palpable circumscribed noncalcified solid breast masses at mammography and US: can biopsy be averted? Radiology. 2004 Dec;233(3):850-6. Epub 2004 Oct 14.
3. Karellas A, Vedantham S. Breast cancer imaging: a perspective for the next decade. Med Phys. 2008 Nov;35(11):4878-97. Review.

Statement: MRI of the breast in case of inconclusive conventional imaging

1. Warner E. The role of magnetic resonance imaging in screening women at high risk of breast cancer. Top Magn Reson Imaging. 2008 Jun;19(3):163-9. Review.
2. DeMartini W, Lehman C. A review of current evidence-based clinical applications for breast magnetic resonance imaging. Top Magn Reson Imaging. 2008 Jun;19(3):143-50. Review.

Statement: Pelvic examination

Expert Opinion

Routine Follow-Up Examinations in Asymptomatic Patients (11/17)

Further information:

Performing additional tests for recurrence and/or distant metastases screening after primary treatment of breast cancer has shown to reduce disease free survival but does not influence overall survival. Based on current evidence, the AGO discourages additional follow-up examinations in asymptomatic patients, but encourages the performance of future studies on the relevance of additional tests in the context of modern imaging and treatment modalities.

References:

Statement: Magnetic resonance imaging (MRI) of the breast

1. Warner E. The role of magnetic resonance imaging in screening women at high risk of breast cancer. *Top Magn Reson Imaging*. 2008 Jun;19(3):163-9. Review.
2. DeMartini W, Lehman C. A review of current evidence-based clinical applications for breast magnetic resonance imaging. *Top Magn Reson Imaging*. 2008 Jun;19(3):143-50. Review.

Statement: Routine biochemistry (incl. tumor markers)

1. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, Somerfield MR, Hayes DF, Bast RC Jr; American Society of Clinical Oncology. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol*. 2007 Nov 20;25(33):5287-312. Epub 2007 Oct 22. Review
2. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol*. 2005 Dec 20;23(36):9067-72.

Statement: Ultrasound of the liver

1. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distanto V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. *JAMA* 271: 1593–1597
2. Rojas,MP et al: Follow-up strategies for women treated for early breast cancer. Review. *The Cochrane Library* 4 (2004) 1-16.
3. The GIVIO Investigators (1994) Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. *JAMA* 271: 1587–159

4. Grunfeld E, Mant D, Yudkin P et al. Routine follow up of breast cancer in primary care: randomised trial BMJ 1996;313:665-669 (14 September)
5. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol. 2003 Jun;30(3):338-48. Review.

Statement: Bone scan

1. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 271: 1593–1597
2. Rojas,MP et al: Follow-up strategies for women treated for early breast cancer. Review. The Cochrane Library 4 (2004) 1-16.
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4. E. Grunfeld, D. Mant, P. Yudkin et al. Routine follow up of breast cancer in primary care: randomised trial BMJ 1996;313:665-669 (14 September)
5. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol. 2003 Jun;30(3):338-48. Review.

Statement: Chest X-ray

1. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 271: 1593–1597
2. Rojas,MP et al: Follow-up strategies for women treated for early breast cancer. Review. The Cochrane Library 4 (2004) 1-16.
3. The GIVIO Investigators (1994) Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 271: 1587–159
4. E. Grunfeld, D. Mant, P. Yudkin et al. Routine follow up of breast cancer in primary care: randomised trial BMJ 1996;313:665-669 (14 September)
5. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol. 2003 Jun;30(3):338-48. Review.

Statement: CT of chest, abdomen and pelvis

1. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 271: 1593–1597
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5. Emens LA, Davidson NE. The follow-up of breast cancer. *Semin Oncol*. 2003 Jun;30(3):338-48. Review.

Statement: Detection of isolated/circulating tumor cells

1. Janni W, Wiedswang G, Fehm T, Jückstock J, Borgen E, Rack B, Braun S, Sommer H, Solomayer EF, Pantel K, Nesland JM, Frieze K, Naume B. Persistence of disseminated tumor cells (DTC) in bone marrow (BM) during Follow-up predicts increased risk for relapse – Update of the pooled European data. 2006.
2. Rack B, Schindlbeck C, Schneeweiss A, Hilfrich J, Lorenz W, Beckmann MW, Pantel K, Lichtenegger W, Sommer H, Janni W. Prognostic relevance of circulating tumor cells (CTCs) in peripheral blood of breast cancer patients before and after adjuvant chemotherapy: The German SUCCESS-Trial. 2008.

Statement: PET

1. Vranjesevic D, Filmont JE, Meta J, Silverman DH, Phelps ME, Rao J, Valk PE, Czernin J. Whole-body (18)F-FDG PET and conventional imaging for predicting outcome in previously treated breast cancer patients. *J Nucl Med*. 2002 Mar;43(3):325-9.
2. Moon DH, Maddahi J, Silverman DH, Glaspy JA, Phelps ME, Hoh CK. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. *J Nucl Med*. 1998 Mar;39(3):431-5.
3. Ide M. Cancer screening with FDG-PET. *Q J Nucl Med Mol Imaging*. 2006 Mar;50(1):23-7.
4. Schöder H, Gönen M. Screening for cancer with PET and PET/CT: potential and limitations. *J Nucl Med*. 2007 Jan;48 Suppl 1:4S-18S. Review.

Statement: Whole body MRI

1. Vranjesevic D, Filmont JE, Meta J, Silverman DH, Phelps ME, Rao J, Valk PE, Czernin J. Whole-body (18)F-FDG PET and conventional imaging for predicting outcome in previously treated breast cancer patients. *J Nucl Med*. 2002 Mar;43(3):325-9.
2. Layer G, Rieker O, Dörr D, Schnakenberg D, Steudel A, Reiser M. [MR tomography and bone marrow scintigraphy in the screening of skeletal metastases in patients with breast carcinoma] *Rofo*. 1994 May;160(5):448-52. German.

Early Detection of Potentially Curable Events (12/17)

Further information:

Locoregional recurrences include chest wall recurrences, in-breast-recurrences and other locoregional recurrences (tumor spread in the internal mammary, supraclavicular, infraclavicular, ipsilateral axillary nodes or in the non-breast skin of the ipsilateral chest wall). All other sites of tumor recurrence are classified as distant metastases (DM). The early detection of locoregional recurrences represent a potentially curable situation. A total of 30-40% of potentially treatable relapses are detected by patient self-examination. In studies published before 2000, 15% of such relapse is mammographically detected with 46% detected by routine clinical examination. In those published after 2000, 40% are mammographically detected with 15% detected on routine clinical examination. Mammography detected primaries are more likely to be noninvasive, low tumor stage and node negative. MRI could be useful in patients with unclear mammography and / or ultrasound findings.

References:

Statement incidence:

1. Wapnir IL, Anderson SJ, Mamounas EP et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006; 24:2028-2037.
2. Perry NM: Quality assurance in the diagnosis of breast disease. EUSOMA Working Party. Eur J Cancer 2001; 37: 159-172.

Statement breast self examination:

1. Khatcheressian JL, Wolff AC, Smith TJ: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Montgomery DA, Krupa K, Cooke TG Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer. 2007 Dec 17;97(12):1632-41.
3. Thomas DB, Gao DL, Ray RM et al: Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002 Oct 2;94(19):1445-57.

Statement physical examination, mammography & US:

1. Montgomery DA, Krupa K, Cooke TG: Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer. 2007 Dec 17;97(12):1632-41.

2. Beinart G, Gonzalez-Angulo AM, Broglio K: Clinical course of 771 patients with bilateral breast cancer: characteristics associated with overall and recurrence-free survival. Clin Breast Cancer. 2007 Dec;7(11):867-74.
3. Samant R et al. Diagnosis of metachronous contralateral breast cancer. Breast J 2001; 7:405-410
4. Mellink W et al. The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. Cancer 1991, 67:1844-1848
5. Kollias R et al. Prognostic significance of synchronous and metachronous bilateral breast cancer. World J Surg 2001; 25:117-1124
6. Belli P. et al. Magnetic resonance imaging in breast cancer recurrence. Breast Cancer Res Treat 2002; 73:
7. Khatcheressian JL, Wolff AC, Smith TJ: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.

Early Detection of Potentially Curable Events (13/17)

Further information:

Breast cancer patients have an increased risk for contralateral breast cancer (CBC). Young patients with BC treated with tangential breast irradiation experience increased risk of CBC. Adjuvant chemotherapy seems to reduce the risk of CBC during the first 5 years after treatment only. Contralateral breast cancer is diagnosed with more favorable prognostic factors when physical examination and mammography is used during follow-up of breast cancer. Mammography detected primaries are more likely to be noninvasive, low tumor stage and node negative. Annual mammography, routine physical examination and patient self-examination are recommended surveillance to detect IBTR while it can be cured by salvage surgery. MRI should be used to distinguish recurrent tumor from benign post-therapeutic changes in the treated breast.

References:

Statement risk and incidence:

1. Yerushalmi R, Kennecke H, Woods R, Does multicentric/multifocal breast cancer differ from unifocal breast cancer? An analysis of survival and contralateral breast cancer incidence. Breast Cancer Res Treat. 2008 Dec 11. [Epub ahead of print]
2. Hoening MJ, Aleman BM, Hauptmann M: Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer J Clin Oncol. 2008 Dec 1;26(34):5561-8.
3. Bertelsen L, Møller L, Christensen J: Age-Specific Incidence of Breast Cancer in Breast Cancer Survivors and Their First-Degree Relatives. Epidemiology. 2008 Dec 1. [Epub ahead of print]

Statement breast self examination:

1. Khatcheressian JL, Wolff AC, Smith TJ: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.
2. Montgomery DA, Krupa K, Cooke TG: Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer. 2007 Dec 17;97(12):1632-41.
3. Thomas DB, Gao DL, Ray RM et al: Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst. 2002 Oct 2;94(19):1445-57.

Statement physical examination, mammography & US:

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4. Mellink W et al. The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. Cancer 1991, 67:1844-1848
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Early Detection of Potentially Curable Events (14/17)

Further information:

There is a significantly increased risk of several kinds of second malignancy in women treated for BC, compared with the general population. These may be due to a co-incidence (ovary), similar mechanisms in carcinogenesis (endometrium), treatment side effects (endometrium), genetic or unknown associations (colon). Patients with breast cancer should be screened for secondary malignancies according to current guidelines. Pelvic examination and PAP smear a recommended every 6 months. The impact of imaging diagnostics is questionable, even in high risk patients. Routine transvaginal sonography or hysteroscopy with biopsy increase the number of interventions in benign changes without proven effects of early detection of malignant disease.

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Statement: Risk:

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Statement: Screening for secondary malignancies according to current guidelines

1. Khatcheressian JL, Wolff AC, Smith TJ: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7.

Statement: Pelvic examination and PAP smear

1. Rieck GC, Lim K, Rogers MT: Screening for familial ovarian cancer--management and outcome of women with moderate to high risk of developing ovarian cancer. *Int J Gynecol Cancer*. 2006 Jan-Feb;16 Suppl 1:86-91
2. Chan JK, Manuel MR, Cheung MK: Breast cancer followed by corpus cancer: is there a higher risk for aggressive histologic subtypes? *Gynecol Oncol*. 2006 Sep;102(3):508-12.
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5. Mahon SM, Williams MT, Spies MA: Screening for second cancers and osteoporosis in long-term survivors. *Cancer Pract*. 2000 Nov-Dec;8(6):282-90

Statement: Endometrial ultrasound / biopsy

1. Gerber B, Krause A, Müller H, Reimer T: Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. *J Clin Oncol*. 2000 Oct 15;18(20):3464-70.
2. Barakat RR, Gilewski TA, Almadrones L: Effect of adjuvant tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy. *J Clin Oncol*. 2000 Oct 15;18(20):3459-63.
3. Fung MF, Reid A, Faught W: Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. *Gynecol Oncol*. 2003 Oct;91(1):154-9.

Follow-Up Care for Breast Cancer (incl. LCIS/DCIS) (15/17)

Further information:

Following these guidelines improves:

- diagnosis of contralateral breast cancer, IBTRs, chest wall recurrences while curable
- improves the detection of treatment related complications and distant disease and
- avoids unnecessary, expensive and potentially harmful tests.

There is no evidence to suggest that clinical examination confers a survival disadvantage compared with other methods of detection. A third of patients may wish to maintain a regular review. There is no clear evidence to recommend a follow-up three monthly. Some guidelines recommended 3 to 6 monthly. It has been shown that after 2 years following the diagnosis of breast cancer there is no evidence to support the view that regular clinical review improves psychological morbidity or quality of life. Patients do not appear to be compromised in terms of early detection of recurrence. Point of need access can be provided by suitably trained specialist nurses and provides a fast, responsive management system at a time when patients really need it. Follow-up of women with LCIS or DCIS includes interval history and physical examinations every 6 to 12 months for five years and then annually, as well as yearly diagnostic mammography. In Patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed 6-12 months after the completion of breast conserving radiation therapy.

This table summarizes a consensus by the AGO.

References:

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3. Montgomery DA, Krupa K, Cooke TG: Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer. 2007 Dec 17;97(12):1632-41.
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Breast Cancer Follow-up Duration. Breast Nurses (16/17)

Further information:

The accumulating evidence of the potential benefit that may be achieved by prolonged endocrine therapy, suggests longer surveillance of these patients. Especially in patients with ER-positive disease, recurrence frequently occur after year 5.

The goals of follow-up as perceived and reported by the patients comprises

- Examination of the breast
- Reassurance
- Guidance of patients, answering questions
- Evaluation of treatment and treatment of side effects
- Psychosocial support.

These goals may be similarly or better achieved by specialized breast nurses. International trials have shown equivalence between physician's and nurses' surveillance. Clinical trials should test this also with regard to the German health care situation.

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1. van Hezewijk M, Ranke GM, van Nes JG, Stiggelbout AM, de Bock GH, van de Velde CJ. Patients' needs and preferences in routine follow-up for early breast cancer; an evaluation of the changing role of the nurse practitioner. Eur J Surg Oncol. 2011 Sep;37(9):765-73.
2. Sheppard C. Breast cancer follow-up: literature review and discussion. Eur J Oncol Nurs. 2007 Sep;11(4):340-7.

Luminal-like, HER2-positives and triple-negative breast cancer patients (17/17)

Further information:

Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence. ER-positive patients have stable risk over many years requiring long term surveillance, However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.

References:

1. Ribelles N, Perez-Villa L, Jerez JM, Pajares B, Vicioso L, Jimenez B, de Luque V, Franco L, Gallego E, Marquez A, Alvarez M, Sanchez-Muñoz A, Perez-Rivas L, Alba E. Pattern of recurrence of early breast cancer is different according to intrinsic subtype and proliferation index. Breast Cancer Res. 2013 Oct 22;15(5):R98.



Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Loco-regional Recurrence

Loco-regional Recurrence

- **Version 2002:**
Brunnert / Simon
- **Versions 2003–2013:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Lisboa / Mundhenke /
Rezai / Solomayer / Souchon / Thomssen**
- **Version 2014:**
Dall / Maass

Loco-regional Recurrence Incidence and Prognosis

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| Localization | Frequency (%) | 5-y. Overall Survival (%) |
|--|------------------|------------------------------|
| Ipsilateral recurrence¹ (post BCT + irradiation) | 10 (2–20) | 65 (45–79) |
| Chest wall¹ (post mastectomy) | 4 (2–20) | 50 (24–78) |
| As above plus supraclavicular fossa² | 34% | 49% (3-y. OS) |
| Axilla: | | |
| After ALND¹ | 1 (0.1–8) | 55 (31–77) |
| After SNB⁴ | 1 | 93% |
| Multiple localizations² | 16 (8–19) | 21 (18–23) |

¹ Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991; ²Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 2011; ³Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978; ⁴Andersson Y, et al. Br J Surg 99(2):226-31,2012

Loco-regional Recurrence Staging

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Examinations before treatment:

| | | | |
|--------------------------------|----------|----------|-----------|
| ➤ Tissue Biopsy | 5 | D | ++ |
| ➤ Reassessment of ER, PR, HER2 | 5 | D | ++ |
| ➤ Complete re-staging | 5 | D | ++ |

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Loco-Regional Recurrence Risk Factors at Primary Diagnosis

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Increased risk for loco-regional recurrence

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- | | |
|---|-----|
| ➤ Young age | 1a |
| ➤ Positive microscopic margins | 1a |
| ➤ Number of involved lymph nodes | 1a |
| ➤ Omitting adjuvant radiotherapy (if indicated) | 1a |
| ➤ Extensive intraductal component | 1b |
| ➤ Vessel invasion | 1b |
| ➤ Triple negative and HER2 / HR- vs. HR+ | 2a |
| ➤ Grading (G3 vs. G1) | 1b* |
| ➤ Elevated proliferation markers: partic. Ki67 | 2b |
| ➤ pT (> 2 vs. ≤ 2cm) | 1b* |
| * node negative | 1a |
| ➤ pN (N1 vs. N0) | 1a |
| ➤ Inflammatory breast cancer | 2b |
| ➤ Medial tumor localisation (vs. central/lateral) | 4 |

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Metaanalysis: TNBC and Local Recurrence

Wang et al., Surg Oncol 2013 (Epub)

n = 15312 BC-patients, 22 studies, Hazard-ratios

| | | | |
|------|------------------|-----|---------------|
| | BCT | vs. | ME |
| ILRR | 0.75 (0.65-0.87) | | |
| DM | 0.68 (0.60-0.76) | | |
| | TNBC-subtype | vs. | other subtype |
| ILRR | 1.88 (1.58-2.22) | | |
| DM | 2.12 (1.72-2.62) | | |
| | TNBC-subtype | vs. | HER2-subtype |
| ILRR | 0.69 (0.53-0.91) | | |
| DM | n.s. | | |

ILRR: ipsilateral locoregional recurrence

DM: distant metastasis

TNBC: triple negative breast cancer

BCT: breast conserving therapy ME: mastectomy

Risk Factors for Locoregional Recurrences after ME

Karlsson et al. Ann Oncol 23:2852-8, 2012

IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence ...:

...>15% chest wall: age <40; ≥ 4 pos. nodes, 0-7 uninvolved nodes

...>10% supraclavicular: ≥ 4 pos. nodes

...>5% axillary failure: age <40; unknown tumor size, 0-7 uninvolved nodes

Metaanalysis: 7174 BCT and 5418 ME

Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after Breast Cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 133(3):831-41, 2012

After BCT:

HR-positive tumors show a lower risk for LRR than...
triple negative tumors (RR 0.38) and....
HER2-expressing tumors (RR 0.34)

After ME:

HR-positive tumors show a lower risk for LRR than...
HER2- expressing tumors (RR 0.69) and...
triple negative tumors (RR 0.61)

Result:

HR-positive tumors exhibit the lowest rate of local recurrence.

Loco-regional Recurrence Prognostic / Predictive factors

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Parameters in local recurrence to define risk for re-recurrence

- Tumor size
- Multifocality
- Localisation
- Parameters in local recurrence to define risk
for distant metastasis/survival
- Early (<2-3 yrs.) vs. late recurrence
- LVSI/Grade/ERneg/close margin
(if ≥ 2 factors pos.)

2a B

2a B

2b B

2b B

3b B

Predictive factors for treatment considerations

- HER2
- ER and PgR

2b B

++

2b B

++

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

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Panet-Raymond V et al., Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. Cancer 117:2035, 2011

n=6020 pat., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:

TTR <48 months

LVSI (of the LRR)

ER negative LR-tumor

high grade

close margins of recurrent tumor

=> if ≥ 2 factors positive => worse OS

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Ipsilateral Recurrence after BCT Surgery

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- **Mastectomy (aim: R0)**
- **Re-BCS with tumor-free margins
± flap reconstruction**
 - Disadvantage for overall survival cannot be excluded
 - Impaired cosmetic result cannot be ruled out
 - Impaired local tumor control cannot be fully excluded
- **Axillary intervention after prior AxDissection if cN0**
- **SNE after prior SNE if cN0***
- **Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial)**

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3b B ++

3b C +/-

4 C -

4 D +/-

5 D +

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* If no sentinel lymph node could be identified, axillary dissection is not recommended

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

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- **Curative situation: R0-resection**
- **Palliative situation: Resection of
deep parts of the chest wall**
- **Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial)**

2b A ++

5 D +/-

5 D +

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Loco-regional Recurrence after R0-Resection

Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

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- Endocrine therapy in endocrine responsive tumors
- Chemotherapy (consider neoadjuvant)
- In case of HER2 positive disease
Chemotherapy + HER2 targeted therapy

2b **B** **++**

2b **B** **+**

5 **D** **+**

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Cytotoxic Treatment in Pts with Local Recurrent Breast Cancer

➤ CALOR Trial – Overall Survival

Kein Unterschied bei ER-/ER+
Unabhängiger prognostischer Marker!

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Aebi et al. SABCS 2012

Locoregional Recurrence in Case R0

Resection not Likely - Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

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- | | | | |
|---|----|---|----|
| ➤ Endocrine therapy in endocrine responsive tumors | 2b | B | ++ |
| ➤ Chemotherapy (pre- or postoperatively) | 2b | B | ++ |
| ➤ HER2-targeted therapy in HER2-overexpressing tumors(+ chemotherapy) | 1b | A | ++ |

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Ipsilateral Recurrence after BCT Radiotherapy

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After Re-BCS

- Whole breast irradiation
(in case adjuvant radiotherapy was not performed)
- Re-breast irradiation
(Partial breast radiation, brachytherapy,
external beam RT)

3b C ++

3b C +/-

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
(14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)

2b B +/-

3b C -

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy

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Chest-Wall Recurrence after Mastectomy

- If no prior postmastectomy radiotherapy
 - Curative situation: irradiation of the chest wall +/- regional lymph nodes
- Re-irradiation (chest wall + hyperthermia)

| | | |
|-----------|----------|------------|
| 2b | B | + |
| 1b | B | +/- |

Axillary recurrence

Irradiation of axilla after R0-surgery

- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

| | | |
|-----------|----------|------------|
| 3b | C | + |
| 5 | D | -/+ |

Loco-Regional Recurrence

Treatment Options

in Non Curative Cases

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| | | | |
|---|----|---|-----|
| ➤ Topical chemotherapy (miltefosine) | 3b | C | + |
| ➤ Concomitant radio-chemotherapy | 3b | C | + |
| ➤ Hyperthermia (in centers listed on DKG website) | | | |
| ➤ In combination with radiotherapy | 1b | B | + |
| ➤ In combination with chemotherapy | 4 | C | +/- |
| ➤ Intra-arterial chemotherapy | 4 | C | +/- |
| ➤ Photodynamic therapy | 4 | C | +/- |
| ➤ Electrochemotherapy | 3b | C | +/- |

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Loco-regional Recurrence (2/18)

Further information:

Screened data bases: Pubmed 2005 - 2012, ASCO 2005 – 2013, SABCs 2009 – 2013, Cochrane data base

Guidelines:

Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012

NCCN (National Comprehensive Cancer Network, 2012);

http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (download 13. Jan. 2013)

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms
Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL;

http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf

No references

Loco-regional Recurrence Incidence and Prognosis (3/18)

Further information:

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

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Loco-regional Recurrence Staging (4/18)

Further information:

The 5-year overall survival of patients with isolated loco-regional recurrence amounted to 50%. There are no data about the frequency of distant metastases detected by modern staging examinations at time of recurrence. Moreover there are no studies confirming a implication of the re-staging findings in systemic treatment or improvement of overall survival of asymptomatic patients with resectable loco-regional recurrence. Nevertheless to avoid „over- or undertreatment“ and to prevent complications the AGO recommends a re-staging in all patients with resectable recurrences.

References:

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Loco-regional Recurrence Risk Factors at Primary Diagnosis (5/18)

Further information:

Risk factors for IBTR include tumor size, nodal status, estrogen receptor status, molecular subtype, young age, positive microscopic margins, extensive intraductal component, higher grading, vessel invasion multifocality, an extensive intraductal component, and lymphatic vessel invasion. Multivariate analysis stratified by treatment showed that age was an independent prognostic factor for local control. Systemic treatment and radiation therapy significantly reduced local recurrence.

References:

Statement: Increased risk for loco-regional recurrence

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Statement: Young age

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Statement: Positive microscopic margins

1. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ: Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 42(3):351-6, 2006
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
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4. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 21: 1205–1213, 2003

Statement: Extensive intraductal component

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
2. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997

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4. Cheng SH et al.: Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 64(5):1401-9, 2006

Statement: Vessel invasion

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
2. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 21: 1205–1213, 2003
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Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors

1. van der Hage JA, Mieog JS, van de Velde CJ, Putter H, Bartelink H, van de Vijver MJ Impact of established prognostic factors and molecular subtype in very young breast cancer patients:pooled analysis of four EORTC randomized controlled trials. *Breast Cancer Res Breast Cancer Res* 24;13(3):R68, 2011
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3. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
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Statement: Grading (G3 vs. G1)

1. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ: Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 42(3):351-6, 2006
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Statement: pT (> 2 vs. ≤ 2cm)

1. Yildirim E, Berberoglu U: Local recurrence in breast carcinoma patients with T(1-2) and 1-3 positive nodes: indications for radiotherapy. *Eur J Surg Oncol* 33(1):28-32, 2007
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials *Lancet* 366: 2087–2106, 2005

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Statement: pT (> 2 vs. ≤ 2cm) and Grading (G3 vs. G1) in node negative

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
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3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 21: 1205–1213, 2003
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6. Livi L, Paiar F, Simontacchi G, Barca R, Detti B, Fondelli S, Bastiani P, Santini R, Scotti V, Bianchi S, Cataliotti L, Mungai V, Biti G. Loco regional failure pattern after lumpectomy and breast irradiation in 4,185 patients with T1 and T2 breast cancer. Implications for nodal irradiation. *Acta Oncol*. 45: 564-70, 2006

Statement: pN (N1 vs. N0)

1. Yildirim E, Berberoglu U: Local recurrence in breast carcinoma patients with T(1-2) and 1-3 positive nodes: indications for radiotherapy. *Eur J Surg Oncol* 33(1):28-32, 2007
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5. Jagsi R, Raad RA, Goldberg S, Sullivan T, Michaelson J, Powell SN, Taghian AG. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 62(4):1035-9, 2005
6. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 64(5):1401-9, 2006
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Statement: number of involved lymph nodes

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
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3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 21: 1205–1213, 2003
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6. Crawford JD, Ansteth M et al. Routine completion axillary lymph node dissection for positive sentinel nodes in patients undergoing mastectomy is not associated with improved local control. *Am J Surg* 205: 581-4, 2013

Statement: Medial tumor localisation (vs. central/lateral)

1. Knauerhase H, Strietzel M, Gerber B, Reimer T, Fietkau R. Tumor location, interval between surgery and radiotherapy and boost technique influence local control after breast conserving surgery and radiation: retrospective analysis of monoinstitutional long-term results. *Int J Radiat Oncol Biol Phys* 72: 1048-55, 2008

Statement: elevate proliferation marker, esp. Ki67

1. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol* 28(10):1684-91, 2010

Statement: Inflammatory breast cancer

1. Saigal K, Hurley J et al. Risk factors for locoregional failure in patients with inflammatory breast cancer treated with trimodality therapy. *Clin Breast Cancer* 13:335-43, 2013

Statement: Nomograms

1. Tsoutsou PG, Jeanneret Sozzi W et al. Nomograms predicting locoregional recurrence in the subtype era of breast cancer. *J Clin Oncol* 31: 647-8, 2013

2. After neoadjuvant chemotherapy: Manounas EP, Anderson SJ, Dignam JJ et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of NASBP B-18 and B-27. J Clin Oncol 30: 3960-6, 2012
3. Kraeima J, Siesling S, Vliegen IM et al. Individual risk profiling for breast cancer recurrence: towards tailored follow-up schemes. Br J Cancer 109: 866-71, 2013

Metaanalysis: TNBC and Local Recurrence (6/18)

No further information

No references

Risk Factors for Locoregional Recurrence after ME (7/18)

No further information

No references

Metaanalysis: 7174 BCT and 5418 ME (8/18)

No further information

No references

Loco-regional Recurrence Prognostic/Predictive factors (9/18)

No further information

References:

Parameters in local recurrence to define risk for re-recurrence

Statement: Tumour size

1. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006
2. Lannin DR, Haffty BG. End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

Statement: Multifocality

1. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006

Statement: Localisation

1. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. Int J Radiat Oncol Biol Phys 64(5):1401-9, 2006
2. Lannin DR, Haffty BG.: End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

Statement : Early vs. Late recurrence

1. Lee JS, Kim SI, Park HS, Lee JS, Park S, Park BW. The impact of local and regional recurrence on distant metastasis and survival in patients treated with BCT. J Breast Cancer 14:191-7, 2011
2. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 23(2):285-91, 1992
3. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 4(13):2028, 2006

LVSI/Grade/ERneg/close margins

1. Panet-Raymond V, Truong PT, Alexander C, Lesperance M, McDonald RE, Watson PH. Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. Cancer 117:2035, 2011

Predictive factors for treatment considerations

Statement: HER-2

1. Clemons M, Hamilton T, Goss P. Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001

Statement: ER and PR

1. Clemons M, Hamilton T, Goss P. Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001
2. Haffty BG, Reiss M, Beinfeld M, Fischer D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol 14: 52–57, 1996
3. Kuo SH, Huang CS, Kuo WH, Cheng AL, Chang KJ, Chia-Hsien Cheng J. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Oncology Biol Phys 72: 1456-64, 2008

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence (10/18)

No further information

No references

Ipsilateral Recurrence after BCT - Surgery (11/18)

Further information:

Mastectomy is the current standard of care for ipsilateral recurrence of breast carcinoma. Some retrospective analyzes showed that second conservative treatments for local relapse were feasible and gave results comparable to standard mastectomy. A repeat BCT demands tumor free margins and an interstitial brachytherapy. However, the indication for second lumpectomy is restricted for suited patients (small-size, low-risk). As data from prospective randomized clinical trials are missing, an impaired regional tumor control (without disadvantages for overall survival) cannot be ruled out completely. In patients with distant metastases a local surgery is indicated in pain, endangered ulceration and in some cases for psychological reasons. Reoperative SLNB after previous axillary surgery is technically feasible after breast conserving therapy. In case no sentinel lymph node can be identified, axillary dissection is not recommended.

References:

Statement: Mastectomy (aim: R0)

1. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
2. Shin E, Suemasu K, Sonoo H, Taguchi T, Nishi T, Nishimura R, Haga S, Mise K, Kinoshita T, Murakami S, Yoshimoto M, Tsukuma H, Inaji H: Analysis of ipsilateral breast tumor recurrences after breast-conserving treatment based on the classification of true recurrences and new primary tumors. Breast Cancer 12(2):104-11, 2005

Statement: Re-BCS with tumor-free margins ± flap reconstruction

1. Kuerer HM Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast irradiation. Cancer 100(11):2269-80, 2004

2. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005

Statement: disadvantage for overall survival cannot be excluded, poor cosmetic result, impaired local tumor control

1. Kuerer HM Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast irradiation. Cancer 100(11):2269-80, 2004

Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0

1. Intra M, Trifirò G, Viale G, Rotmensz N, Gentilini OD, Soteldo J, Galimberti V, Veronesi P, Luini A, Paganelli G, Veronesi U. Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 12(11):895- 899, 2005
2. Taback B, Nguyen P, Hansen N, Edwards GK, Conway K, Giuliano AE. Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. Ann Surg Oncol 13(8):1099-104, 2006
3. Port ER, Garcia-Etienne CA, Park J, Fey J, Borgen PI, Cody HS 3rd: Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. Ann Surg Oncol. 14(8):2209-14, 2007
4. Derkx F, Maaskant-Braat AJ, van der Sangen MJ, Nieuwenhuijzen GA, van de Poll-Franse LV, Roumen RM, Voogd AC. Staging and management of axillary lymph nodes in patients with local recurrence in the breast or chest wall after a previous negative sentinel node procedure. Eur J Surg Oncol 36(7):646-51, 2010
5. Barone JL, Feldman SM, Estabrook A, Tarter PI, Rosenbaum Smith SM, Boolbol SK: Reoperative sentinel lymph node biopsy in patients with locally recurrent breast cancer. Am J Surg 194(4):491-3, 2007

Statement: Palliative surgery in M1-situation

1. Rapiti E. et al.: Complete Excision of Primary Breast Tumor Improves Survival of Patients With Metastatic Breast Cancer at Diagnosis. Journal of Clinical Oncology 2743-2749, 2006

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Sugery (12/18)

Further information:

Because chest wall recurrences are not infrequently a marker of concurrent or future metastatic disease, local management with curative intent is advocated only after thorough re-staging.

References:

Statement: Curative situation: R0-resection

1. Mignano JE, Gage I, Piantadosi S, Ye X, Henderson G, Dooley WC: Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007

Statement: Palliative situation: Resection of deep parts of the chest wall

1. Mignano JE, Gage I, Piantadosi S, Ye X, Henderson G, Dooley WC: Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007
2. Pfannschmidt J, Geisbüsch P, Muley T, Hoffmann H, Dienemann H.: Surgical resection of secondary chest wall tumors. Thorac Cardiovasc Surg 53(4):234-9, 2005

Statement: Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)

1. Rapiti E. et al.: Complete Excision of Primary Breast Tumor Improves Survival of Patients With Metastatic Breast Cancer at Diagnosis. Journal of Clinical Oncology 2743-2749, 2006

Locoregional Recurrence after R0-Resection - Systemic Treatment (13/18)

Further information:

Systemic therapy after resected local recurrence (readjuvant) is associated with improved disease-free and overall survival. Endocrine treatment in hormone sensitive tumors improves disease free survival. The impact on overall survival has not been proven.

References:

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, Jungi WF, Thürlimann B, Cavalli F, Obrecht JP. First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research. J Clin Oncol. 12(10):207, 1994
2. Lê MG, Arriagada R, Spielmann M, Guinebretière JM, Rochard F. Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma. Cancer 94(11):2813-20, 2002
3. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B Locoregional recurrence of breast cancer: a retrospective comparison of irradiation alone versus irradiation and systemic therapy. Am J Clin Oncol. 15(2):93-101, 1992

Statement: Chemotherapy

1. Wapnir IL, Aebi S, Gelber S, Anderson SJ, Láng I, Robidoux A, Mamounas EP, Wolmark N. Progress on BIG 1-02/IBCSG 27-02/NSABP B-37, a prospective randomized trial evaluating chemotherapy after local therapy for isolated locoregional recurrences of breast cancer. Ann Surg Oncol 15(11):3227-31, 2008
2. Easson AM, McCready DR: Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004

3. Rauschecker H, Clarke M, Gatzemeier W, Recht A. Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4):CD002195. Review.
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Statement: Trastuzumab - based therapy in HER-2 overexpressing tumors

So far, extrapolations from adjuvant Her2-directed studies and from studies in metastatic breast cancer

1. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL; http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf

Cytotoxic Treatment in pts with Local Recurrent Breast Cancer (14/18)

No further information

No references

Locoregional Recurrence in case R0-resection not likely - Systemic Treatment (15/18)

No further information

References:

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, Jungi WF, Thürlimann B, Cavalli F, Obrecht JP. First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research. J Clin Oncol. 12(10):207, 1994
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Statement: Chemotherapy (pre- or postoperatively)

1. Kuo SH et al. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiat Oncol Biol Phys 72: 1456-64 (2008)
2. Tokunaga Y, Hosogi H, Nakagami M, Tokuka A, Ohsumi K.: A case of chest wall recurrence of breast cancer treated with paclitaxel weekly, 5'-deoxy-5-fluorouridine, arterial embolization and chest wall resection. Breast Cancer. 2003;10(4):366-70.
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7. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17Version 3.2012
8. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012

Statement: Trastuzumab based therapy in HER-2 overexpressing tumors

So far, extrapolations from adjuvant Her2-directed studies and from studies in metastatic breast cancer.

Ipsilateral recurrence after BCT - Radiotherapy (16/18)

Further information:

Repeat irradiation breast for recurrent breast cancer is feasible. If no prior radiotherapy has performed after BCS, whole breast radiation should be performed. In patients with no prior radiotherapy after mastectomy irradiation of chest wall and regional lymph nodes is recommended.

References:

Statement: Whole breast radiation

1. McCready DR, Fish EB, Hiraki GY, Ross TM, Wall JL, Lickley HL. Total mastectomy is not always mandatory for the treatment of recurrent breast cancer after lumpectomy alone. *Can J Surg* 35(5):485 :485-8, 1992
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL; http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf
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4. Skinner HD, Strom EA Motwani SB et al. Radiation dose escalation for locoregional recurrence of breast cancer after mastectomy. *Radiat Oncol* 8: 13, 2013

Statement: Re-irradiation (breast)

1. Hannoun-Levi JM et al.: Partial breast irradiation as second conservative treatment for local breast cancer recurrence. *Int J Radiat Oncol Biol Phys* 60(5):1385-92, 2004
2. Kuerer HM Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast irradiation. *Cancer* 100(11):2269-80, 2004

3. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 63(3):845-51, 2005
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Statement: Curative situation: irradiation of the chest wall +/- regional lymph nodes

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. *Int J Radiat Oncol Biol Phys*. 2007 Sep 13

Chest-wall recurrence / Axillary recurrence - radiotherapy (17/18)

No further information

References:

Statement: If no prior postmastectomy radiotherapy

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. Int J Radiat Oncol Biol Phys 70(2):477-84, 2008

Statement: Re-irradiation (chest wall + hyperthermia)

1. Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL: Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: a review of the randomised data. Int J Hyperthermia 26(7):612-7, 2010
2. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, van Putten WLJ, van Rhoon GC, van Dijk JDP, Gonzalez Gonzalez D, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: Results from five randomized controlled trials. Int J Radiat Oncol Biol Phys 35:731-744, 1996

Statement Axillary recurrence

1. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17; Version 3.2012
2. Konkin DE, Tyldesley S, Kennecke H, Speers CH, Olivotto IA, Davis N Arch Surg. Management and outcomes of isolated axillary node recurrence in breast cancer 141(9):867-72, 2006
3. Newman LA, Hunt KK, Buchholz T, Kuerer HM, Vlastos G, Mirza N, Ames FC, Ross MI, Singletary SE. Presentation, management and outcome of axillary recurrence from breast cancer. Am J Surg 180:252-256, 2000

Loco-Regional Recurrence - Treatment Options in Non-Curative Cases (18/18)

Further information:

The combination of chemotherapy and hyperthermia (HT) is a promising approach in the treatment of malignant tumors. Local hyperthermia combined with radiotherapy may be effective in the treatment of locally recurrent breast cancer, especially for previously irradiated cases, where only a reduced total irradiation dose is applicable. Care should be taken, to select experienced providers that treat accordingly to recognised guidelines. While the combination of hyperthermia and radiotherapy has been used for several decades and shown its efficacy in prospective randomized trials, the combination of chemotherapy and hyperthermia (HT) has much less intensively been studied in breast cancer. Few recent papers report on trimodal therapeutic attempts: chemotherapy, radiotherapy plus hyperthermia, the additional benefit of chemotherapy is not quite clear.

References:

Statement: Topical chemotherapy (miltefosine)

1. Leonard R, Hardy J, van Tienhoven G, Houston S, Simmonds P, David M, Mansi J. Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. J Clin Oncol 19(21): 4150–4159, 2001

Statement: Concomitant radio-chemotherapy

1. McCormick B: Counterpoint: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):345 – 8, 2007
2. Jones EL, Marks LB, Prosnitz LR: Point: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):339-44, 2007

Statement: Hyperthermia + radiotherapy +/- chemotherapy

1. McCormick B: Counterpoint: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):345 – 8, 2007
2. Jones EL, Marks LB, Prosnitz LR: Point: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):339-44, 2007
3. Bischoff J, Lindner LH, Issels RD, Costa S: Clinical impact of locoregional hyperthermia in gynecological oncology. Zentralbl Gynakol 128(5):255-60, 2006
4. Zoul Z: Weekly paclitaxel combined with local hyperthermia in the therapy of breast cancer locally recurrent after mastectomy--a pilot experience. Onkologie. 27(4):385-8, 2004
5. Li G: Local hyperthermia combined with external irradiation for regional recurrent breast carcinoma. Int J Clin Oncol. 9(3):179-83.
6. Oldenburg S, Van Os RM, Van rij CM, Crezee J, Van de Kamer JB, Rutgers EJ, Geijssen ED, Zum vörde sive vörding PJ, Koning CC, Van tienhoven G.: Elective re-irradiation and hyperthermia following resection of persistent locoregional recurrent breast cancer: A retrospective study. Int J Hyperthermia 26(2):136-44, 2010
7. Vujaskovic Z, Kim DW, Jones E, Lan L, McCall L, Dewhirst MW, Craciunescu O, Stauffer P, Liotcheva V, Betof A, Blackwell K. . A phase I/II study of neoadjuvant liposomal doxorubicin, paclitaxel, and hyperthermia in locally advanced breast cancer Int J Hyperthermia 26(5):514-21, 2010
8. Kouloulis VE, Koukourakis GV, Petridis AK, Kouvaris I, Gouliamos AD. The efficacy of caelyx and hyperthermia for anticancer treatment. Recent Pat Anticancer Drug Discov 2(3):246-50, 2007
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10. Feyerabend T, Wiedemann GJ, Jäger B, Vesely H, Mahlmann B, Richter E. Local hyperthermia, radiation, and chemotherapy in recurrent breast cancer is feasible and effective except for inflammatory disease. Int J Radiat Oncol Biol Phys Apr 1;49(5):1317-25, 2001

Statement: Intraarterial chemotherapy

1. Murakami M, Kuroda Y, Nishimura S, Sano A, Okamoto Y, Taniguchi T, Nakajima T, Kobashi Y, Matsusue S. Intraarterial infusion chemotherapy and radiotherapy with or without surgery for patients with locally advanced or recurrent breast cancer. Am J Clin Oncol 24(2):185-91, 2001

Statement: Photodynamic therapy

1. Allison R, Mang T, Hewson G, Snider W, Dougherty D. Photodynamic therapy for chest wall progression from breast carcinoma is an underutilized treatment modality. Cancer 91(1):1-8,2001.
2. Wyss P, Schwarz V, Dobler-Girdziunaite D, Hornung R, Walt H, Degen A, Fehr M. Photodynamic therapy of locoregional breast cancer recurrences using a chlorin-type photosensitizer Int J Cancer. 93(5):720-4, 2001

Statement: Electrochemotherapy

1. Campana LG, Valpione S, Falci C, Mocellin S, Basso M, Corti L, Balestrieri N, Marchet A, Rossi CR. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Res Treat 134(3):1169-78, 2012
2. Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 51(6):713-21, 2012
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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Endocrine and “Targeted” Therapy in Metastatic Breast Cancer

Endocrine Therapy of Metastatic Breast Cancer

➤ **Version 2002:**

Gerber / Friedrichs

➤ **Versions 2003–2013:**

**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat / Kaufmann /
Loibl / Lück / von Minckwitz / Müller / Nitz /
Schneeweiß / Stickeler**

➤ **Version 2014:**

Mundhenke / Schütz

Endocrine Therapy in Metastatic Breast Cancer

Indication

Oxford LoE: 1a

GR: A

AGO: ++

**Endocrine therapy represents the first choice
for metastatic breast cancer with positive
(unknown) hormone receptor status.**

- **Exception: acute life threatening disease**
- **Cave: HR might change during the course of the disease. Histology of recurrent site should be obtained, whenever possible**

Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor

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| Publication | Number of patients | ER % | PgR% | HER2% |
|--------------|--------------------|------|------|-------|
| Prospektiv | | | | |
| Thompson | 137 | 10 | 25 | 3 |
| Amir | 94 | 14 | 40 | 10 |
| Retrospektiv | | | | |
| Lindström | 459 | 33 | 40 | 14 |
| Niikura | 182 | - | - | 24 |
| | | | | |

Changes from primary tumor to metastatic disease

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Further
Information

References

Endocrine Therapy

in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer

| | Oxford / AGO LoE / GR | | |
|---|--------------------------|----------|------------|
| ➤ GnRHa + tamoxifen (vs. OFS or Tam) | 1a | A | ++ |
| ➤ Ovarian function suppression (OFS) | 2b | B | + |
| ➤ Tamoxifen | 2b | B | + |
| ➤ GnRHa + AI (first or second line) | 2b | B | + |
| ➤ GnRHa + Fulvestrant | 4 | C | +/- |
| ➤ Aromatase inhibitors without OFS | 3 | D | -- |

Endocrine Therapy

in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer

Treatment options for postmenopausal patients pretreated with adjuvant tamoxifen or without adjuvant endocrine therapy

- Aromatase inhibitors (3rd gen) (> non-AI*)
- Tamoxifen (vs. no therapy)
- Fulvestrant 500 mg
- Fulvestrant 250 mg (= AI)
- MPA/MA (< AI)
- Fulvestrant 250 mg + Anastrozol (vs. Ana)

Oxford / AGO
LoE / GR

| | | |
|----|---|-----|
| 1a | A | ++ |
| 1a | A | ++ |
| 1b | B | ++ |
| 2b | B | + |
| 1a | A | +/- |
| 1b | B | +/- |

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus + exemestane are indicated after AI treatment, a non-steroidal AI should be preferred in first line.

Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no Prior Endocrine Treatment

Treatment sequence

| | | Oxford / AGO LoE / GR | | |
|-----------------------|----------------------------------|--------------------------|---|-----|
| 1 st line: | aromatase inhibitors (3rd gen)* | 1a | A | ++ |
| | fulvestrant 250 mg + anastrozole | 2b | C | +/- |
| 2 nd line: | fulvestrant | 1b | B | |
| | fulvestrant 500 mg | 1b | B | ++ |
| | fulvestrant 250 mg | 2b | B | +/- |
| | exemestane + everolimus | 1b | A | ++ |
| | tamoxifen | 3b | C | + |
| | aromatase inhibitor** | 2b | B | + |
| | tamoxifen + everolimus | 2b | B | + |
| Further | MPA/MA | 4 | D | +/- |
| Lines: | estradiol 6 mg daily | 3b | C | +/- |
| | repeat prior treatments | 5 | D | +/- |

* To date, there is no evidence for superiority of a single aromatase inhibitor.

** steroidal or non-steroidal depending on previous AI

Therapy Algorithm After Adjuvant Tamoxifen

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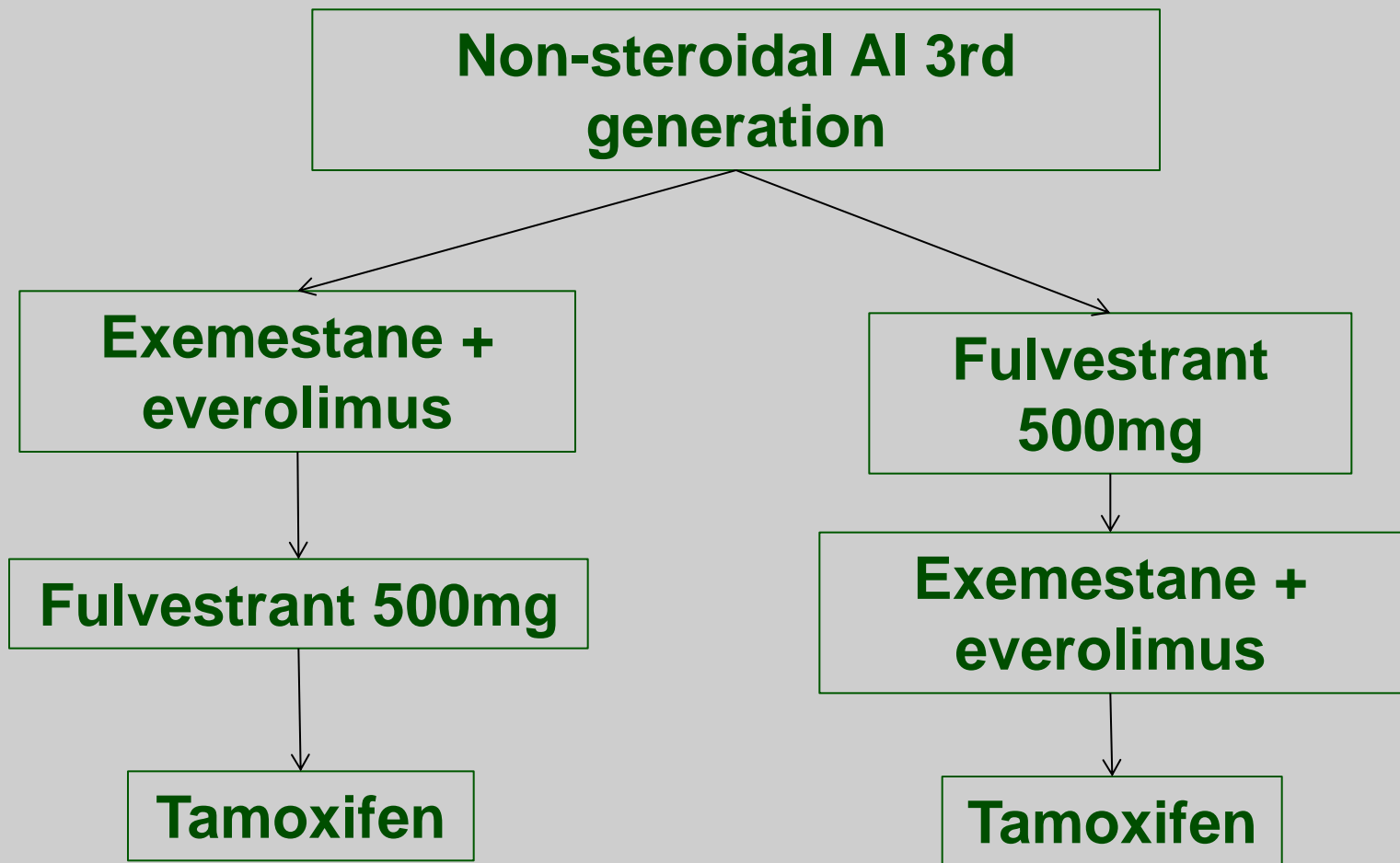
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Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant AI

Treatment sequence

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LoE / GR

1st line:

| | | | |
|--|----|---|----|
| ➤ tamoxifen | 2b | B | ++ |
| ➤ fulvestrant 500 mg | 1b | B | ++ |
| ➤ exemestane + everolimus* (relapse within 12 mths) | 1b | A | ++ |
| ➤ steroidal after non-steroidal AI non-steroidal after steroidal AI | 2b | B | + |
| ➤ tamoxifen + everolimus | 2b | B | + |

2nd line:

| | | | |
|---------------------------------------|----|---|----|
| ➤ fulvestrant 500 mg | 1b | B | ++ |
| ➤ exemestane + everolimus* | 1b | A | ++ |
| ➤ tamoxifen (if previously not given) | 5 | D | + |
| ➤ tamoxifen + everolimus | 2b | B | + |

Further lines:

| | | | |
|---------------------------|---|---|-----|
| ➤ MPA/MA | 4 | C | +/- |
| ➤ repeat prior treatments | 5 | D | +/- |

*After pretreatment with at least a non-steroidal AI in the metastatic and/or adjuvant setting

**trial participation

Therapy Algorithm After Adjuvant AI

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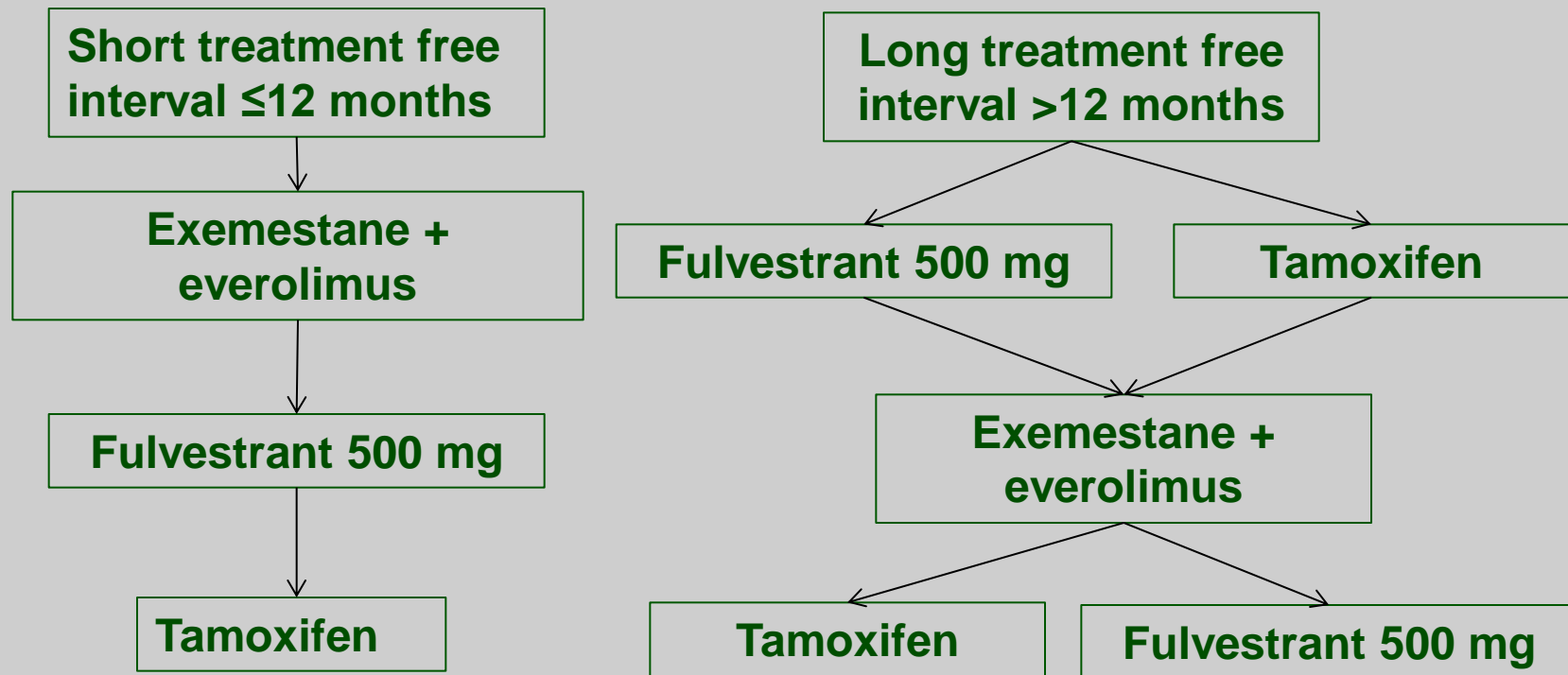
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HER2 Positive and HR-Positive Metastatic Breast Cancer

Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients

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- **Anastrozole and trastuzumab**
- **Letrozole and trastuzumab**
- **Letrozole and lapatinib**
- **Fulvestrant and lapatinib**

**Oxford / AGO
LoE / GR**

| | | |
|-----------------------|----------|------------|
| 1b | B | +/- |
| 2b | B | +/- |
| 1b | B | +/- |
| 1b^a | B | - |

**Poor efficacy of endocrine therapy alone.
Consider chemotherapy + anti-HER2-therapy!**

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Further
Information

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Combination of Endocrine Treatment with Anti-HER2-Treatment

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| Treatment (no. of pats) | PFS (mo) | Response (CBR) | OS (mo) |
|--|---|-------------------|------------------------|
| Trastuzumab + anastrozole vs. anastrozole (n=207) | 4.8 vs. 2.4 (5.6 vs. 3.8 with central confirmed receptor status) | 42.7% vs. 27.9% | 28.5 vs. 23.9 mo; n.s. |
| Trastuzumab + letrozole vs. letrozole (n=57) | 14 vs. 3.3 | 27% vs. 13% | n.r. |
| Lapatinib + letrozole vs. letrozole (n=219/1286) | 8.2 vs. 3.0 | 48% v 29% | 33.3 vs. 32.3 mo |
| Lapatinib + fulvestrant vs. fulvestrant (n=267/324) | 5.2 vs. 4.0 (all) 5.9 vs. 2.8 (HER2+) | | 22.3 vs. 21.9 (all) |

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Concomitant or Sequential Endocrine-Cytostatic Treatment

Oxford / AGO
LoE / GR

➤ Concomitant endocrine-cytotoxic treatment

1b A - -

- Increases response rates without prolongation of progression free interval or overall survival
- Increases toxicity

➤ Maintenance endocrine therapy after chemotherapy induced response

3 C ++

- Increases progression free interval

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Endocrine Therapy of Metastatic Breast Cancer (2/14)

Further information:

Search:

Medline, PubMed Central 12/2012-01/2013

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Gibson L, Lawrence D, Dawson C, Bliss J. Aromataseinhibitor for treatment of advanced breast cancer in postmenopausal women. Cochrane, Wiley 2009, Issue 4

Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy versus endocrine therapy alone for metastatic breast cancer, Cochrane, Wiley 2011, Issue 7

NICE. Advanced breast cancer. Full Guideline Februar 2009, National Collaborating Center for Cancer, Cardiff, Wales UK, p1-122

Fleemann N, Bagust A, Boland A, Dickson R, Dunder Y, Moonan M, Oyee J, Blundell M, Davis H, Armstrong A, and Thorp N: Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor-positive breast cancer which over-expresses human epidermal growth factor 2 (HER2): a systematic review and economic analysis. Health Technol Assess 2011;15:1-100

Cardoso F, Fallowfield L, Costa A, Castiglione M, Senkus E on behalf of the ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22 (Suppl. 6): v25-v30

Endocrine Therapy in Metastatic Breast Cancer – Indication (3/14)

Further information:

Endocrine therapy as the first choice in hormone receptor positive breast cancer

Endocrine therapy remains the most important approach to the treatment of hormone-sensitive non-life-threatening metastatic breast cancer. This systemic therapy has the advantage of combining efficacy, minimal toxicity, and good quality of life. Endocrine therapy use in clinical practice is based on a positive estrogen receptor (ER) and/or progesterone receptor status of the primary tumour or, if at all possible, of an easily accessible metastasis. This type of therapy is usually the first choice when the risk of rapid disease progression is low, i.e. if there is no life-threatening disease. The selection of the most appropriate endocrine therapy takes into account the receptor status of the metastasis, menopausal status of the patient, the type of adjuvant endocrine therapy received, and past medical history of thrombotic disease.

A Cochrane Data Base Meta-Analysis was performed in 2003 whether chemotherapy alone versus endocrine therapy alone for metastatic breast cancer is more favorable.

The primary analysis of overall effect using hazard ratios derived from published survival curves involved six trials (692 women). There was no significant difference seen (HR=0.94, 95%CI 0.79-1.12, p=0.5). A test for heterogeneity was p=0.1. A pooled estimate of reported response rates in eight trials involving 817 women shows a significant advantage for chemotherapy over endocrine therapy with RR=1.25 (1.01-1.54, p=0.04). However the two largest trials showed trends in opposite directions, and a test for heterogeneity was p=0.0018.

There was little information available on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity with chemotherapy, mentioning nausea, vomiting and alopecia. Three of the seven mentioned aspects of quality of life, with differing results. Only one trial formally measured quality of life, concluding that it was better with chemotherapy.

The Reviewers concluded that in women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease (Cochrane 2011).

Responserate to endocrine treatment (De Laurentiis M, et al. 2005):

| ER | PR | Response |
|----------|----------|----------|
| Negative | negative | < 10% |
| Positive | negative | 20 – 30% |
| Negative | positive | 30 – 50% |
| Positive | positive | 50 – 75% |

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Wilcken N, Hornbuckle J, Gheri D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747. Review.

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De Laurentiis M, et al.: A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res. 2005 Jul 1;11(13):4741-8

Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor (4/14)

Further information:

Changes in receptor profiles

Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting.

Several retrospective studies have evaluated this biological phenomenon.

There is evidence for a prognostic impact of receptor profile changes in metastatic breast cancer: In a retrospective analysis, patients with tumors that changed from ER positive primary to negative metastasis experienced a significantly shorter median survival than patients with unchanged receptor profiles, while changes in PR status were not associated with a change in survival. Therefore, optimal metastatic treatment cannot be determined solely on primary ER and PR analyses (Lower et al. 2005).

A published retrospective study (Broom et al. 2009). evaluated data from 100 patients for whom tissue from primary and metastatic sites was available. Estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu status in the primary and metastasis were compared. The discordance rate for ER was 17.7% (2-sided $p=0.0039$) with 9.7% of tumors changing from ER-positive to ER-negative and 8.0% changing from ER-negative to ER-positive. The discordance rate for PR was 37.3% (2-sided $p<0.0001$), with all of these tumors changing from PR-positive to PR-negative. No significant discordance for Her-2/neu was found. This study suggested that significant discordance exists for hormone receptor status between primary and metastatic breast cancer samples. Loss of PR was particularly frequent.

Further evidence was shown by a retrospective analysis of 97 consecutive relapsed patients (Nishimura et al 2011). Changes in the positive/negative evaluation were seen at the rate of 10.3% and 25.8% for ER and PgR. Ki-67 index increased significantly from a mean of 29.1% at primary tumor to 36.6% at relapse. The rates of change in HER2 and p53 positivity were 14.4% and 12.4%. The change of subtypes were seen in 25%, however the lowest rate of change was seen

in the triplenegative cases. A multivariate analysis revealed that the status of distant metastasis and PgR level at relapse, and Ki-67 levels at primary tumor were all significant factors.

One prospective study, BRITS (Breast Recurrence In Tissue Study), investigated 137 matched primary and recurrent breast cancer tissue samples. The recurrent biopsy was excisional tissue in 100 (73%) and core biopsy in 37 (27%). Central laboratory analysis of the original primary was ER positive in 109 (79.6%), PR positive in 85 (62.0%) and HER2 positive in 14 (10.2%); the recurrent disease was ER positive in 101 (73.7%), PR positive in 75 (54.7%) and HER2 positive in 16 (11.7%). A switch in receptor status, in either direction, was identified for ER in 14 patients (10.2%; $p=0.983$ Wilcoxon sign rank test), PR in 34 (24.8%; $p=0.003$ Wilcoxon sign rank test) and HER2 in 4 (2.9%; $p=0.074$ Wilcoxon sign rank test). There was no difference between locoregional or distant recurrence in the proportion who switched. In the judgement of the investigators the switch led to a change in the subsequent treatment in 24 patients (17.5%).

This study demonstrated that the management of locally recurrent or metastatic breast cancer should include tissue sampling, since switches of ER, PR or HER2 status in the breast cancer recurrence may change the planned treatment for one in six patients (Thompson 2010).

However if treatment guided by the new ER,PR or HER2 status of the metastasis is superior when findings are different to the primary tumor has not been investigated so far.

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Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer (5/14)

Further information and references:

GnRHa + tamoxifen

The combination of GnRH + tamoxifen represents the first choice as endocrine first line therapy of hormone receptor positive premenopausal breast cancer.

Due to the results of one randomized trial and a metaanalysis of additional 4 trials in a three-arm, randomized, prospective trial a total of 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with buserelin, tamoxifen, or both. The median follow-up was 7.3 years. Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate (48%, 34%, and 28% respectively; $P = .11$ [chi(2) test]), median progression-free survival (9.7 months, 6.3 months, and 5.6 months; $P = .03$), and overall survival (3.7 years, 2.5 years, and 2.9 years; $P = .01$). Actuarial 5-year survival percentages were 34.2%, 14.9%, and 18.4%, respectively. No differences in antitumor effects were observed between single-agent treatment groups (Klijn et al. 2000). For patients with solitary bone metastasis a prospective multicenter study on 318 patients revealed even a survival benefit besides a significant improvement of progression free survival (Jonat et al 1995).

The metaanalysis (Klijn et al. 2001) confirmed the above findings in four clinical trials randomizing a total of 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen. With a median follow-up of 6.8 years, there was a significant survival benefit ($P = .02$; hazards ratio [HR] = 0.78) and progression-free survival benefit ($P = .0003$; HR = 0.70) in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment ($P = .03$; odds ratio = 0.67).

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Ovarian function suppression, tamoxifen

A further option in the treatment of metastasized premenopausal hormone receptor positive breast cancer is ovarian ablation. Oophorectomy and GnRHa have been demonstrated to be equally efficacious in the metastatic setting. Taylor et al. evaluated these two methods for premenopausal patients with ER-positive, PR-positive, and unknown hormone status metastatic breast cancer. 136 patients were randomly assigned to either bilateral oophorectomy (n = 67) or goserelin (n = 69). The overall response rate was 31% for those in the goserelin group versus 27% in the oophorectomy group. The complete response (CR) rate for the two arms was 14 and 10%, respectively. The response rates between the two arms were not statistically significant.

An additional randomized, nonblinded trial compared oophorectomy and radiation ablation for metastatic breast cancer, 97 patients were treated with oophorectomy, and 61 had ovarian ablation by radiation. In the oophorectomy arm, 30% had a response (CR + partial response), and 18% had stable disease. In the radiation arm, 21% had a response (CR + partial response), and 15% had stable disease. These differences were not statistically significant (Lees et al. 1980).

Tamoxifen is well established as an alternative to ovarian suppression as first-line treatment for hormone receptor-positive breast cancer in the metastatic setting, especially in case of contraindications against a combination therapy with GnRHa (Oborne 1998). Several studies were reported over the last decade (Ingle et al. 1986, Buchanan et al. 1986, Sawka et al. 1997).

A meta-analysis of randomized trials comparing tamoxifen to ovarian ablation carried out either by surgery or irradiation as first-line hormonal therapy for pre-menopausal women with metastatic breast cancer enrolled 220 patients in four trials. There was no difference in overall response rate between tamoxifen and oophorectomy across the four trials ($p = 0.94$, Mantel-Haenszel test). The odds reduction for progression was 14% \pm 12% and for mortality 6% \pm 13% in favour of tamoxifen, which was not statistically significant ($p = 0.32$ and 0.72 , respectively). Although the design of all four studies included a cross-over to the other therapy, only 54/111 patients receiving ovarian ablation and 34/109 patients receiving tamoxifen as primary therapy actually crossed over to the other arm at the time of disease progression. The efficacy of tamoxifen appears to be similar to that of ovarian ablation by surgery or irradiation as first-line therapy for premenopausal, ER positive metastatic breast cancer (Crump et al. 1997).

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GnRH-A + AI

Even if the evidence is rather limited, aromatase inhibitors can be an option in the treatment of metastatic premenopausal breast cancer.

Based on a Phase II trial (Forward et al. *BR J Cancer* 2004) the combination of GNRHa plus aromatase inhibitors is a second line option after GNRHa + tamoxifen treatment failure.

A total of 16 premenopausal women with metastatic breast cancer (N=13) or locally advanced primary breast cancer (N=3) were treated with a combination of a gonadotropin-releasing hormone agonist goserelin, and a selective aromatase inhibitor anastrozole. All had previously been treated with goserelin and tamoxifen. In all, 12 patients (75%) achieved objective response or durable stable disease at 6 months, with a median duration of remission of 17+ months (range 6-47 months). Four patients still have clinical benefit. Introduction of goserelin and tamoxifen resulted in an 89% reduction in

mean oestradiol levels (pretreatment vs 6 months=224 vs 24 pmol l(-1)) ($P<0.0001$). Substitution of tamoxifen by anastrozole on progression resulted in a further 76% fall (to 6 pmol l(-1) at 3 months) ($P<0.0001$) (Forward et al. 2004).

Additionally there is evidence for GnRHa+ aromatase inhibitors as first line treatment in premenopausal patients. Besides a case study of 3 patients (El-Saghir et al. 2006), a small randomized trial compared GnRHa + anastrozole vs. GnRHa+ tamoxifen in 119 peri/premenopausal women with hormone dependent metastatic breast cancer (Milla-Santos et al.2002). In comparison to GnRHa+tamoxifen the study combination showed higher response rates (80% vs. 53%, $P=0.023$), improved clinical benefit rates ($P=0.05$) as well as prolonged overall survival (18.9 vs. 14.3 months).

A phase II trial (Carlson RW et al JCO 2010) with a cohort of 32 patients with metastatic disease were treated with GnRHa+anastrozole: One participant (3.1%) experienced a complete response, 11 (34.4%) experienced partial response, and 11 (34.4%) experienced stable disease for 6 months or longer for a clinical benefit rate of 71.9%. Median time to progression was 8.3 months (range, 2.1 to 63+) and median survival was not been reached (range, 11.1 to 63+).

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Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer (6/14)

Further information:

In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy. 3rd Generation aromatase agents should be the first endocrine treatment choice in patients with distant metastases of hormone responsive breast cancer and no adjuvant aromatase inhibitor treatment. This is demonstrated in numerous clinical trials and confirmed in a meta-analysis updated in 2009 (see references).

The clinical benefit of tamoxifen for treatment of metastatic breast cancer is shown in numerous trials and tamoxifen remains a mayor treatment option in the metastatic setting despite the superiority of aromatase inhibitors for first line treatment.

Fulvestrant in the dose of 250mg every four weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of MBC. In the recently approved dose of 500mg four weeks it is superior to aromatase inhibitors as second line treatment of MBC.

MPA/MA are options as sequential therapies after other endocrine therapies have been used. However, they seem to be inferior to AI.

Trials comparing aromatase inhibitors for their efficacy have not delivered conclusive results, although one study stated that response with anastrozole was higher compared with letrozole. However, this was not the primary end point of this trial (see references “comparison of different AI”)

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Fulvestrant + Anastrozole

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Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no prior Endocrine Treatment (7/14)

Further information and references:

AI (3rd gen), bevacizumab

Additional aspects not discussed on the previous slide:

- Evidence suggests that switching therapy from non-steroidal to a steroidal AI is as effective as fulvestrant in its approved dose of 250mg/q4 weeks (study “EFFECT”). It seems likely that also the switch from steroidal to non steroidal AI is effective and is therefore a therapeutic option.

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Fulvestrant 500 mg > AI

The “FIRST” trial using the higher dose of 500mg/q4w stated first-line fulvestrant HD was at least as effective as anastrozole for CBR (the primary end point) and ORR, but was associated with significantly longer TTP (a secondary end point) in patients pre-treated with endocrine treatment. A follow up analysis showed an even stronger superiority with a median TTP of 23.4 months for fulvestrant HD and 13.1 months for anastrozole (p=0.01).

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Fulvestrant 500 mg > 250 mg

In addition to the approved dose of 250 mg by intramuscular injection, highdose (HD) regimen of fulvestrant (500 mg once a month plus 500 mg on day 14 of month 1) is associated with a significantly longer progression-free survival (PFS) and can be recommended for patients who had progressed on prior endocrine therapy (Effect Trial, Confirm Trial, Finder I and II Trial).

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Estradiol

In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate of 28% as 30 mg, with fewer serious adverse events.

References:

Ellis MJ, Gao F, Dehdashti F, Jeffe DB, Marcom PK, Carey LA, Dickler MN, Silverman P, Fleming GF, Kommareddy A, Jamalabadi-Majidi S, Crowder R, Siegel BA. Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study. JAMA. 2009 Aug 19;302(7):774-80.

Therapy Algorithm After Adjuvant Tamoxifen (8/14)

No further information

No references

Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant AI (9/14)

Further information:

For patients with progression or relapse after the adjuvant use of an AI Fulvestrant plays an important role for second line treatment.

In the Bolero-2 study a phase 3, randomized trial, everolimus (10mg/die) and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio) was compared in 724 patients with hormone- receptor–positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed. The median age was 62 years, 56% had visceral involvement. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%) and prior chemotherapy for metastatic disease (25%). The number of previous therapies was at least 3 regimens in 54% of the patients. Overall response (0.4 vs 9.5%, $p < 0.0001$) and clinical benefit rate (18 vs 33.4%, $p < 0.0001$) was significantly higher in the combination group versus exemestane alone. Further at interim analysis median PFS was significantly increased with the combination of exemestane and everolimus both by local (2.8 vs 6.9 months, HR 0.43, 95% CI 0.35-0.54, $p < 0.001$) and central assessment (4.1 vs 10.6 months, HR 0.36, 95% CI, 0.27-0.47, $p < 0.001$). The most common grade 3/4 adverse events were stomatitis (8 vs 1%), anemia (4 vs <1%), dyspnea (4 vs 1%), and pneumonitis (3 vs 0%) and more frequently seen with the combination of exemestane and everolimus.

The potential of everolimus to benefit patient survival is not yet known.

In a small randomized phase 2 study 111 patients with hormone receptor positive metastatic disease and prior aromatase inhibitor therapy were randomized to tamoxifen (n=57) or tamoxifen and everolimus (n=54; 10mg/die). The clinical benefit rate (42.1 vs 61.1%, $p=0.045$) time to progression (4.5 vs 8.6 months, HR 0.53, 95% CI 0.35-0.81, $p=0.0026$ exploratory log rank) and overall survival (HR 0.32 95% CI 0.15-0.68, $p=0.0019$) were significantly superior in the combination treatment compared to tamoxifen alone.

References:

Baselga J, Campone M, Piccart M, Burris H, Hope S, Sahmoud T, Noguchi S, Gnant M, Pritchard K, Lebrun F, Beck T, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, XU Z, Mukhopadhyay P, Lebwohl D, and Hortobagyi G: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Eng J Med 2011, (10.1056/NEJMoa1109653): 1-10

Bachelot T, Bourcier C, Croper C, and et al: TAMRAD: a GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients with hormone-receptor positive, HER2 negative metastatic breast cancer with prior exposure to aromatase inhibitor. Annual San Antonio Breast Cancer Symposium, Abstract, Dec 08-10, 2010

Therapy Algorithm After Adjuvant AI (10/14)

No further information

No references

Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients (12/14)

Further information:

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aromatase inhibitor treatment is able to enhance the efficacy over endocrine treatment alone. However, given the relative short progression free interval in the phase III trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients.

One phase III trial comparing fulvestrant + placebo vs. Fulvestrant + lapatinib could not demonstrate an improved PFS or OS in 324 patients pretreated with an AI.

For further information on trials combining endocrine treatment with anti-HER2 therapy, see following slide.

References:

1. Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Révil C, Jones A. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009 Nov 20;27(33):5529-37
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5. Burstein HJ, Barry WT, et al. CALGB 40302: Fulvestrant with or without Lapatinib as Therapy for Hormone Receptor Positive Advanced Breast Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Study. *SABCS 2010*. Abstract.

Combination of Endocrine Treatment with Anti-HER2-Treatment (13/14)

No further information

References:

Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Révil C, Jones A. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol.* 2009 Nov 20;27(33):5529-37.

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Johnston S, Pippen J Jr, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S, Pegram M. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009 Nov 20;27(33):5538-46

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Concomitant or Sequential Endocrine-Cytostatic Treatment (14/14)

Further information:

Concomitant endocrine cytostatic therapy can not be recommended because it induces an increase in toxicity and does not induce a prolongation of disease free interval or overall survival despite the increase of response rates. Thus, endocrine – cytostatic therapy should be performed as sequential treatment modality.

Endocrine mainenance therapy after chemotherapy induced response might be considered, even if the evidence is quite small and not homogeneous, since only relatively little side effects are observed with this sequential treatment option.

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Sledge GW, Hu P, Falkson G, et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An eastern cooperative oncology group study. J Clin Oncol 18, 262-266, 2000.

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Kloke O, Klaassen u; Oberhoff C et al. Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. Essen Breast Cancer Study Group. Breast Cancer Res Treat 55:51-59, 1999.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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 START

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

***Substances are only discussed if there is at least published evidence
on one phase III / IIb study available**

Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

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- **Version 2002:**
von Minckwitz / Schaller / Untch
- **Versions 2003–2013:**
**Bischoff / Dall / Fersis / Friedrichs / Harbeck /
Jackisch / Janni / Möbus / Rody / Scharl /
Schmutzler / Schneeweiss / Schütz / Stickeler
/Thomssen**
- **Version 2014:**
Bischoff / Janni

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Disease-Free and Overall Survival in Metastastatic Breast Cancer

**General observation, not specific for
cytotoxic chemotherapy**

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LoE / GR**

- **An increase in survival over time in MBC has
been shown in retrospective analyses**
- **A survival benefit has been shown in recent
single prospective randomized studies of
combination chemotherapy**
- **Multiple lines of sequential therapy are
beneficial (at least same efficacy, less toxicity)**
- **In some combinations of chemotherapy with
targeted drugs, a relevant survival benefit has
been observed**

2a

1b

1b

1b

Treatment of Metastatic Breast Cancer

Predictive Factors

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| Therapy | Factor | | | |
|----------------------|---|----|---|----|
| Endocrine therapy | ER / PR (primary tumor, metastasis) | 1a | A | ++ |
| | previous response | 2b | B | ++ |
| Chemotherapy | previous response | 1b | A | ++ |
| Anti-HER2-drugs | HER2 (primary tumor, better metastasis) | 1a | A | ++ |
| | | 1a | A | ++ |
| Bone modifying drugs | bone metastasis | 1a | A | ++ |
| Any therapy | CTC monitoring | 1b | A | + |

(other potentially biological factors see chapter „Predictive factors“)

*within clinical trials

Cytotoxic Therapy Goals

Oxford LoE: 1b

GR: A

AGO: ++

Mono-Chemotherapy:

- **Favourable therapeutic index**
- **Indicated in case of**
 - **Slow, not life-threatening progression**
 - **Insensitive to or progression during endocrine therapy**

Poly-Chemotherapy:

- **Unfavourable therapeutic index**
- **Indicated to achieve rapid remission in the case of**
 - **Extensive symptoms**
 - **Imminent life-threatening metastases**
- **Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven**

Therapeutic index evaluates overall efficacy, toxicity and impact on quality of life

Cytotoxic and Targeted Therapy

LoE: 1c

GR: A

AGO: ++

- **Evaluate compliance before and during therapy (especially in elderly patients, with reduced PS, or significant co-morbidities)**
- **Assess subjective and objective toxicities, symptoms and PS repeatedly**
- **Use dosages according to published protocols**
- **Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion might be sufficient. In slow growing disease, longer intervals are acceptable.**

Cytotoxic Therapy Duration

**Oxford / AGO
LoE GR**

As long as therapeutic index remains positive

- | | | | |
|---|-----------|----------|-----------|
| ➤ Treatment until best response | 2b | B | + |
| ➤ Treatment until progression | 2b | B | + |
| ➤ Change to alternative regimen before progression | 2b | B | - |
| ➤ Stop therapy in case of | 1c | A | ++ |
| ➤ Progression | | | |
| ➤ Non-manageable toxicity | | | |

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Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends on:

- **ER / PR, HER2; combination with biologicals**
- **Previous treatments (and their toxicities)**
- **Aggressiveness of disease and localization of metastases**
- **Biologic age**
- **Co-morbidities (including organ dysfunctions)**
- **Patients preference and expectations**

MBC HER2 negative Cytotoxic 1st-Line Therapy*

Oxford / AGO LoE / GR

Monotherapy:

- Doxorubicin, epirubicin, mitoxantrone (A),
Peg. liposomal doxorubicin (A_{lip})
- Docetaxel (q3w), paclitaxel (q1w) (T)
- Vinorelbine
- Capecitabine
- Nab-paclitaxel
- Ixabepilone

| | | |
|----|---|----|
| 1b | A | ++ |
| 1b | A | ++ |
| 3b | B | + |
| 2b | B | + |
| 2b | B | + |
| 1B | B | - |

Polychemotherapy:

- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- T + gemcitabine after adj. A
- (F) + A + C or A_{lip} + C
- CMF(1+8)
- BMF (bendamustine)
- Ixabepilone + capecitabine

| | | |
|-----------------|---|-----|
| 1b | A | ++ |
| 2b ^a | B | + |
| 1b | A | + |
| 2b | B | ++ |
| 1b | B | ++ |
| 2b | B | +/- |
| 1b | B | +/- |
| 1b | B | +/- |

*In ER pos. disease only if endocrine therapy is not or not anymore indicated

MBC HER2 negative: Cytotoxic Therapy after *Anthracycline* Treatment*

- Docetaxel q3w
- Paclitaxel q1w
- Capecitabine
- Nab-paclitaxel
- Peg-liposomal doxorubicin
- Vinorelbine
- Docetaxel + Peg-liposomal Doxo
- Etoposid / cisplatinum

Oxford / AGO LoE / GR

| | | |
|----|---|-----|
| 1a | A | ++ |
| 1a | A | ++ |
| 2b | B | ++ |
| 2b | B | ++ |
| 2b | B | + |
| 2b | B | + |
| 1b | B | +/- |
| 2b | B | +/- |

***independent whether anthracyclines were used in adjuvant
or 1st line metastatic situation**

MBC HER2 negative: Cytotoxic Therapy After *Taxane and Anthracycline Treatment*

Oxford / AGO LoE / GR

| | | | |
|---|----|---|-----|
| ➤ Experimental therapies within studies | | | ++ |
| ➤ Capecitabine | 2b | B | ++ |
| ➤ Eribulin | 1b | B | ++ |
| ➤ Vinorelbine | 2b | B | ++ |
| ➤ (Peg)-liposomal Doxorubicin | 2b | B | + |
| ➤ Gemcitabine + Cisplatin / Carboplatin | 2b | B | +/- |
| ➤ Gemcitabine + Capecitabine | 2b | B | +/- |
| ➤ Gemcitabine + Vinorelbine* | 1b | B | - |
| ➤ Ixabepilone + Capecitabine* | 1b | B | - |

***Cave neutropenia / therapeutic index!**

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-)

**Oxford / AGO
LoE / GR**

- **Cytotoxic therapy as for
ER pos. HER2 neg. patients** ++
- **Experimental therapies within studies** ++
- **Platinum-based regimen** 4 C +/-
- **Bevacizumab added to cytotoxic
therapy** 2b B +

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Targeted Agents Registered in Other Indications – Potentially Effective in HER2 negative BC

| | Oxford / AGO LoE / GR | | |
|--|--------------------------|---|-----|
| ➤ Sorafenib | 1b | B | - |
| ➤ Sunitinib | 1b | B | - |
| ➤ Ramucirumab added to cytotoxic therapy | 1b ^a | B | -* |
| ➤ Vandetanib | 1b | B | --* |

* Study participation recommended

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

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➤ 1st line in combination with:

- Paclitaxel (q1w)
- Capecitabine
- Anthracyclines
- Nab-Pac
- Docetaxel (q3w)

| | | |
|----|---|-----|
| 1b | B | + |
| 2b | B | + |
| 2b | B | +/- |
| 2b | B | +/- |
| 1b | B | +/- |

➤ 2nd line in combination with:

- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

| | | |
|----|---|-------|
| 1b | B | +/-* |
| 1b | B | +/- * |
| 1b | B | - |

***Study participation recommended**

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

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| | | | |
|--|-----------------|---|-------|
| ➤ Docetaxel + trastuzumab + pertuzumab | 1b | A | ++ |
| ➤ Paclitaxel + trastuzumab + pertuzumab | 5 | D | + |
| ➤ T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment) | 2b | B | + |
| ➤ 1 st -Line chemotherapy* + trastuzumab | 1b | B | + |
| ➤ Trastuzumab mono | 2b | B | +/- |
| ➤ Taxanes + lapatinib | 1b ^a | B | +/- |
| ➤ Trastuzumab + aromatase inhibitors (if ER+) | 2b | B | +/-** |
| ➤ Lapatinib + aromatase inhibitors (if ER+) | 2b | B | +/-** |

*Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel

**see Chapter Endocrine +/- targeted

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab)

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- **T-DM 1**
- **Capecitabine + lapatinib**
- **Trastuzumab + lapatinib (HR neg. disease)**
- **TBP: 2nd-line chemotherapy + trastuzumab**
- **Taxane + trastuzumab + pertuzumab**
- **Any other 2nd-line chemotherapy* +
trastuzumab + pertuzumab**

**Oxford / AGO
LoE / GR**

1b A ++

1b B +

2b B +

2b D +

5 D +

5 D +/-

- **Trastuzumab + aromatase inhibitors (if ER+)**
- **Lapatinib + aromatase inhibitors (if ER+)**

3b B +

3b B +

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

Further
Information

References

Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

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Pretreatment with Trastuzumab

- T-DM 1
- Capecitabine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Chemotherapy* + trastuzumab + („treatment beyond progression“)
- Trastuzumab + pertuzumab
- Vinorelbine + trastuzumab + everolimus

| | | |
|----|---|-----|
| 1b | A | ++ |
| 1b | B | + |
| 2b | B | + |
| 2b | B | + |
| 2b | B | + |
| 1b | B | +/- |

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen

5 D +**

For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.

5 D

There is no data for treatment beyond progression for pertuzumab.

Trastuzumab in HER2-positive Metastatic Breast Cancer

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➤ As Monotherapy

- After cytotoxic pretreatment
- As 1st line therapy

| | | |
|----|---|----|
| 1b | A | ++ |
| 2b | B | + |

➤ As combination therapy

- With taxanes (1st line)
- With paclitaxel / carboplatin
- Vinorelbine (first line)
- Capecitabine / docetaxel
- Other cytotoxic agents
- In combination with aromatase inhibitors

| | | |
|----|---|-----|
| 1b | A | ++ |
| 1b | A | ++ |
| 1b | B | ++ |
| 1b | B | + |
| 2b | A | + |
| 2b | B | +/- |

➤ As treatment beyond progression

- With capecitabine
- With lapatinib for heavily pre-treated pts.

| | | |
|----|---|---|
| 1b | B | + |
| 2b | B | + |

Duration and dosing of treatment:

- Start of treatment as early as possible
- Treatment until progression of disease
- Weekly or 3weekly

| | | |
|----|---|----|
| 2b | B | ++ |
| 1b | A | ++ |
| 2b | C | ++ |

Lapatinib in HER2-positive Metastatic Breast Cancer

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LoE / GR

In combination with

- Paclitaxel in 1st line
- Capecitabine in $\geq 2^{\text{nd}}$ line
- AI in ER positive disease
- Trastuzumab for heavily
pre-treated pts

2b B +/-

1b B +

2b B +/-

2b B +

- In patients with brain metastases
(radioresistance) in combination
with capecitabine

2b B +/-

Palliative High Dose Chemotherapy

Oxford / AGO
LoE / GR

➤ **High dose-therapy**
(No treatment outside studies)

1a A - -

➤ **Dose dense therapy**
(No treatment outside studies)

1a A - -

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Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer (2/20)

Further information and references:

Update 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).

Screened Sources:

Pubmed 1.12.2012 -15.1.2013

S3-Leitlinie

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2013:

International Guidelines

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Disease-Free and Overall Survival in Metastatic Breast Cancer (3/20)

Further information and references:

As shown in recent single prospective randomized studies survival can be significantly prolonged even in metastatic disease. If outcome in clinical trials over various time periods is compared, survival of patients with metastatic breast cancer has become longer and longer (Gennari et al. Cancer 2005) These observations strongly support the use of cytotoxic therapy in this stage of disease.

It also could be demonstrated that also in metastatic breast cancer it might be worth to keep the relative dose intensity as high as possible. (Loibl et al. ASCO 2009)

Treatment of Metastatic Breast Cancer - Predictive Factors (4/20)

Further information and references:

Prädiktive Faktoren helfen den voraussichtlichen Erfolg einer spezifischen Therapie zuverlässig vorherzusagen. Die Verwendung solcher Faktoren erscheint nur dann sinnvoll, wenn ihre klinische Bedeutung auf höchstem Niveau validiert ist. Die relevanten tumorbiologischen Prädiktoren beim metastasierten Mammakarzinom entsprechen im wesentlichen denen beim primären Mammakarzinom. Voraussetzung für die Wirkung einer endokrinen Therapie ist der Nachweis der Hormonrezeptoren. Bei prämenopausalen Patientinnen mit hormonrezeptorpositiven Tumoren ist die ovarielle Suppression eine wirksame endokrine Therapieoption (GnRH-Agonisten + Tamoxifen evtl. Aromatasehemmer) In der Postmenopause stellen Aromatasehemmer den ersten endokrinen Therapieschritt dar. Eine 2nd line Hormontherapie ist nur dann indiziert, wenn die Patientin auf die erste endokrine Therapie angesprochen hat.

Der Nachweis einer HER-2-Überexpression ist Voraussetzung für eine Therapie mit Trastuzumab. Als Bestimmungsmethode sind die Immunhistochemie im Sinne der Routinemethode und die Fluoreszenz in situ Hybridisierung (FISH) bei zweifach positiven oder unklarem IHC-Befund etabliert. Die Bestimmung von HER-2 im Serum korreliert mit ICH/FISH ist aber derzeit noch nicht ausreichend validiert. In prospektiv randomisierten Studien konnte für Patientinnen mit MBC eine Verlängerung des DFS als auch des OAS sowohl für eine Herceptin-Monotherapie als auch für eine Kombinationstherapie Herceptin/Chemotherapie.

Die Bisphosphonate stellen für die ossären Metastasen als häufigste Organmanifestation eines MBC dar. Die Therapie sollte bei apparativem Nachweis lytischer Knochendestruktionen mit lokalisierten Knochenschmerzen begonnen werden. Eine lebensverlängernde Wirkung von Bisphosphonaten wurde in der metastasierten Situation nicht nachgewiesen. (Hilner et al. 2003 JCO)

Cytotoxic Therapy Goals (5/20)

Further information and references:

Monotherapy has a better therapeutic index than polychemotherapy. Monochemotherapy is indicated if progression is slow and not life threatening or if endocrine therapy becomes ineffective. Polychemotherapy has a less favorable therapeutic index and is indicated if a fast remission should be achieved.

With two exceptions (*O'Shaughnessy et al, 2003, Albain, 2004*) polychemotherapy could not show an advantage over sequential monotherapy with anthracyclines, taxanes, capecitabine, vinorelbin in a prospective randomised study in the last more than 10 years. Life quality tends to be worse under polychemotherapy compared to monochemotherapy.

An example for the similar survival of patients with combination versus monotherapy with the same cytotoxic drugs is a phase 2 study: AP vs A → P vs P → A. (*Sledge et al, 2003*).

A recent meta-analysis found a modest advantage for combination chemotherapy regimens compared with single agents with a hazard ratio (HR) for overall survival of 0.88 (95% CI=0.83-0.94, $P<0.0001$). Combination regimens are favourably associated with time to progression (overall HR of 0.78 (95% CI=0.73-0.83, $P<0.00001$) and tumour response rates (OR 1.28, CI=1.15-1.42, $P<0.00001$)

(S Carrick et al, The Cochrane Database of Systematic Reviews 2005)

2013

Combination vs single agent

Qi WX, Tang LN, He AN, Shen Z, Yao Y. Comparison between doublet agents versus single agent in metastatic breast cancer patients previously treated with an anthracycline and a taxane: A meta-analysis of four phase III trials. *Breast*. 2012 Aug 14. [Epub ahead of print] – no OS advantage

Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C; Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in

metastatic breast cancer. J Cancer Res Clin Oncol. 2012 Feb;138(2):221-9. doi: 10.1007/s00432-011-1091-0. Epub 2011 Nov 18. - no OS advantage

Docetaxel alone or in combination

Metaanalysis; MBC

Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.

Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C; Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. J Cancer Res Clin Oncol. 2012 Feb;138(2):221-9.

Single trials:

Combination not superior compared to single agent regimen.

Pallis AG, Boukovinas I, Ardavanis A, Varthalitis I, Malamos N, Georgoulas V, Mavroudis D.

A multicenter randomized phase III trial of vinorelbine/gemcitabine doublet versus capecitabine monotherapy in anthracycline- and taxane-pretreated women with metastatic breast cancer. Ann Oncol. 2012 May;23(5):1164-9.

Tailored therapy in MBC

Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.

Hatschek T, Carlsson L, Einbeigi Z, Lidbrink E, Linderholm B, Lindh B, Loman N, Malmberg M, Rotstein S, Söderberg M, Sundquist M, Walz TM, Hellström M, Svensson H, Åström G, Brandberg Y, Carstensen J, Fernö M, Bergh J.

Individually tailored treatment with epirubicin and paclitaxel with or without capecitabine as first-line chemotherapy in metastatic breast cancer: a randomized multicenter trial. Breast Cancer Res Treat. 2012 Feb;131(3):939-47.

Cytotoxic and Targeted Therapy (6/20)

Further information:

Before chemotherapy, patients compliance should be evaluated. The chemotherapy effect is less if patients healths condition is affected, if metastases progress and depends on previous therapies. Under therapy objective and subjective toxicity evaluation should be performed. The dosage should be according to published protocols. A lead parameter (metastases, tumor marker, symptoms) should be assessed before therapy and two monthly to evaluate therapeutic effects

References:

2013

International Guidelines

Cardoso F, Costa A, Norton L, Cameron D, Cufer T, Fallowfield L, Francis P, Gligorov J, Kyriakides S, Lin N, Pagani O, Senkus E, Thomssen C, Aapro M, Bergh J, Di Leo A, El Saghir N, Ganz PA, Gelmon K, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Leadbeater M, Mayer M, Rodger A, Rugo H, Sacchini V, Sledge G, van't Veer L, Viale G, Krop I, Winer E. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast. 2012 Jun;21(3):242-52.

Cytotoxic Therapy Duration (7/20)

Further information:

Chemotherapy should be given as long as the therapeutic index is positive, eg until progress or toxicity. Intermittent therapy is superior to cytostatic maintenance therapy. Although progression free survival is longer, toxicity is higher and survival is not prolonged. Chemotherapy should be stopped if disease progresses or intolerable side effects occur.

No references

Chemotherapy for MBC – General Considerations: Drug Selection (8/20)

Further information:

The selection of the drugs and drug combinations should take into account patients expectations, general health conditions, aggressiveness of the disease, localisation of metastases and previous therapies.

References:

2013

Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better

Moinpour CM, Donaldson GW, Liepa AM, Melemed AS, O'Shaughnessy J, Albain KS.

Evaluating health-related quality-of-life therapeutic effectiveness in a clinical trial with extensive nonignorable missing data and heterogeneous response: results from a phase III randomized trial of gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer. Qual Life Res. 2012 Jun;21(5):765-75.

Limitations of palliative chemotherapy

Ribeiro JT, Macedo LT, Curigliano G, Fumagalli L, Locatelli M, Dalton M, Quintela A, Carvalheira JB, Manunta S, Mazzearella L, Brollo J, Goldhirsch A. Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: back to the future? Ann Oncol. 2012 Mar;23(3):547-55.

Metaanalyses

HRQOL is one of the key indicators of treatment benefit in advanced breast cancer, but contemporary systemic therapies in this setting do not appear to affect HRQOL differentially.

Adamowicz K, Jassem J, Katz A, Saad ED. Assessment of quality of life in advanced breast cancer. An overview of randomized phase III trials. Cancer Treat Rev. 2012 Aug;38(5):554-8.

MBC HER2 negative Cytotoxic 1st-Line Therapy* (9/20)

Further information and references:

The most effective drugs in breast cancer are anthracyclines (including liposomal anthracyclines), taxanes and vinorelbine and capecitabine. Therefore these drugs should be used in first line monotherapy.

Metanalysis of 4256 pts. In 12 trials showed single agent A was better than single agent T in terms of PFS, marg. better in terms of RR, no differences in terms of OS. T-based combinations were significantly better than A-based comb. in terms of RR, PFS, but not better in terms of OS (Piccart SABCS 2005).

Liposomal doxorubicin is equally effective to doxorubicin but has less cardio and myelotoxicity but more skin toxicity (*O'Brien et al, 2004*).

Polychemotherapy with anthracyclines and taxanes induce high remission rates but are more toxic then anthracycline or taxane free combinations.

After anthracycline treatment two studies could show a survival benefit with gemcitabine paclitaxel or with Docetaxel/Capecitabine (*O'Shaughnessy et al, 2002 and Albain, 2004*).

Retrospective data show that patients who respond to first line therapy with a complete response have a survival benefit compared to patients without CR (*Greenberg et al, 1996*).

Doxorubicin/docetaxel vs. Doxorubicin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL. Cassier et al., Breast Cancer Research and Treatment (electronic publication 2007).

2013

Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Mayer EL, Naughton M, Layman RM, Carey LA, Somer RA, Perez EA, Hudis C, Winer EP (2012) CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Nab-Paclitaxel

1st line MBC, rand Phase II (n=302)

Treatment with nab-paclitaxel 150 mg/m² qw 3/4 resulted in a median overall survival (OS) of 33.8 months compared with 22.2, 27.7, and 26.6 months for nab-paclitaxel 100 mg/m² qw 3/4, nab-paclitaxel 300 mg/m² q3w, and docetaxel, respectively (overall P = .047).

A trend toward a longer OS was noted in the 150 mg/m² nab-paclitaxel arm versus docetaxel arm (hazard ratio, 0.688). Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms compared with docetaxel.

Gradishar WJ, Krasnojon D, Cheporov S, Makhson AN, Manikhas GM, Clawson A, Bhar P, McGuire JR, Iglesias J. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: final analysis of overall survival. Clin Breast Cancer. 2012 Oct;12(5):313-21.

Ixabepilone + capecitabine vs capecitabine alone in 1st line MBC

Jassem J, Fein L, Karwal M, Campone M, Peck R, Poulart V, Vahdat L. Ixabepilone plus capecitabine in advanced breast cancer patients with early relapse after adjuvant anthracyclines and taxanes: a pooled subset analysis of two phase III studies. Breast. 2012 Feb;21(1):89-94.

Results: In 293 patients, ixabepilone plus capecitabine, as compared to capecitabine alone, increased PFS (median: 5.6 months vs. 2.8 months; hazard ratio, 0.58; p < 0.0001), ORR (46% vs. 24%) and OS (median: 15.1 months vs. 12.5 months; hazard ratio, 0.84; p = 0.208). Major toxicities of this regimen included neuropathy, neutropenia and hand-foot syndrome, but were manageable.

Metaanalyses

Docetaxel alone or in combination

Metaanalysis; MBC

Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.

Belfiglio M, Fanizza C, Tinari N, Ficarella C, Iacobelli S, Natoli C; Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO). Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. J Cancer Res Clin Oncol. 2012 Feb;138(2):221-9.

Batist G, Ramakrishnan G, Sekhar Rao C et al (2001) Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized multicenter trial of metastatic breast cancer J. Clin Oncol 19: 1444-1454

MBC HER2 negative: Cytotoxic Therapy after *Anthracycline* Treatment* (10/20)

Further information and references:

Suggested after anthracyclines (in alphabetical order): Capecitabine, Docetaxel, study-integrated experimental therapies, Gemcitabine, Pegliposomales Doxorubicin, Paclitaxel and Vinorelbine.

As monotherapy after anthracyclin-pretreatment only Docetaxel improved OAS as compared to a standard treatment arm in a prospective randomized trial in metastatic breast cancer (*Nabholtz et al, 1999*).

A Cochrane-metaanalysis of taxane treatment in metastatic breast cancer (*Ghersi et al, 2003*) shows a significant survival advantage as compared to non-taxane-based therapies. There was no significant difference in QoL or treatment related deaths. Final analysis of further end points was difficult due to significant heterogeneity of the single studies.

Indirect and direct comparisons of docetaxel and paclitaxel show a trend towards higher efficacy of docetaxel (*Ghersi et al, 2003; Ravdin et al, 2003*). Due to different toxicity profiles of each substance individual indication is needed.

Docetaxel in Combination with Pegliposomal Doxorubicin was superior to docetaxel alone in a randomised phase III trial by Sparano et al. It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantage from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.

2013

Nab-Paclitaxel

MBC HER2 negative: Cytotoxic Therapy After *Taxane and Anthracycline* Treatment (11/20)

Further information and references:

Nab Paclitaxel (100-150mg/m² d1,8,15,q28) has been tested in different populations. Not all pts received an anthracycline and a taxane. It seems that a weekly dosing is superior to a 3 weekly dosing in terms of efficacy and side effects.

Suggested after anthracycline and taxane treatment (alphabetical order): capecitabine, study-integrated experimental therapies, pegliposomal doxorubicin and vinorelbine.

Studies with more than 100 patients showed overall remissions of 9% and 20% using vinorelbine and pegylated liposomal doxorubicin vs. capecitabine, respectively and a median survival of 9 months and 13 months.

Ixabepilone/Capecitabine vs. Capecitabine after anthracycline and taxane treatment in metastatic breast cancer is a phase III randomised trial showing a significant improvement in PFS for the combination with a higher toxicity especially in neurotoxicity. Ixabepilone is not licensed in Germany; Thomas et al., JCO 25:5210-7 (2007)

Gemcitabine/vinorelbine vs. vinorelbine after anthracycline/taxane treatment in metastatic breast cancer; Martin et al., Lancet Oncol 8:219-25 (2007)

-38 pts treated with Gemcitabine/Cisplatin after anthracycline and taxane pretreatment as (neo)adjuvant, or 1st line met therapy demonstrated a TTP of 5.2 months CI 3.6-6.8 and an OS of 19.5 months CI 11.2-27.8 months. Kim JH; Cancer Res Treat 2008; 40: 101-105

2013

Meta-analysis and evaluation

Eribulin is approved by the Food and Drug Administration for patients with previously treated metastatic breast cancer and has demonstrated a survival benefit compared with standard treatment options in this setting.

Clin Ther. 2012 Jul;34(7):1467-73. doi: 10.1016/j.clinthera.2012.06.003. Epub 2012 Jun 25.

Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer.

Scarpace SL.

New microtubule-targeting agents.

Review

The development of new microtubule-targeting agents helps to address the need for additional effective regimens for patients progressing after standard treatment with anthracycline- and taxane-containing regimens.

Cortes J, Vidal M. Beyond taxanes: the next generation of microtubule-targeting agents. *Breast Cancer Res Treat.* 2012 Jun;133(3):821-30.

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (12/20)

No further information

References:

Triple negative patients

J Clin Oncol 26: 2008 (May 20 suppl; abstr 1051)

Author(s):

B. Sirohi, M. Arnedos, S. Popat, S. Ashley, A. Nerurkar, G. Walsh, S. Johnston, I. E. Smith

Citation:

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 1086

Author(s):

J. W. Chia, P. Ang, H. See, Z. Wong, L. Soh, Y. Yap, N. Wong

2013

Met-TNBC Phase II (n=40; RR 35%, med OS 12 m, med TTP 6 m; 27% neutropenia °3/4)

Halim A, Wahba H. Cisplatin-ifosfamide combination chemotherapy in metastatic triple-negative, anthracycline- and taxane-pretreated breast cancer patients; a phase II study. J BUON. 2012 Apr-Jun;17(2):254-8.

Targeted Agents Registered in Other Indications – Potentially Effective in HER2 negative BC (13/20)

No further information

No references

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (14/20)

Further information and references:

- Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med (2007) 357(26):2666–2676.
- Miles D, Chan A, Luc Y, et al. Phase III Study of Bevacizumab Plus Docetaxel Compared With Placebo Plus Docetaxel for the First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 28:3239–3247, 2010
- Roberts et al., RIBBON-1: Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Chemotherapy With or Without Bevacizumab for First-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative, Locally Recurrent or Metastatic Breast Cancer, J Clin Oncol 29:1252–1260, 2011
- Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol (2005) 23(4):792–799.
- Sledge G, Miller K, Moisa C, Gradishar W. Safety and efficacy of capecitabine (C) plus bevacizumab (B) as first-line in metastatic breast cancer. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 1013
- Brufsky et al., RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy for Second-Line Treatment of Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer, J Clin Oncol 29:4286–4293. 201

2013

Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Mayer EL, Naughton M, Layman RM, Carey LA, Somer RA, Perez EA, Hudis C, Winer EP (2012) CALGB 40502/NCCTG N063H: Randomized phase III trial of weekly

paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Review and opinion

Reddy S, Raffin M, Kaklamani V. Targeting angiogenesis in metastatic breast cancer. Oncologist. 2012;17(8):1014-26. "Despite setbacks, angiogenesis will likely remain an important target of treatment for selected patients with MBC."

Side effects

Metaanalysis:

Cortes J, Calvo V, Ramírez-Merino N, O'Shaughnessy J, Brufsky A, Robert N, Vidal M, Muñoz E, Perez J, Dawood S, Saura C, Di Cosimo S, González-Martín A, Bellet M, Silva OE, Miles D, Llombart A, Baselga J. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Ann Oncol. 2012 May;23(5):1130-7.

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (15/20)

Further information and references:

2013

Docetaxel + trastuzumab + pertuzumab (LoE 1bA AGO++)

Baselga et al., December 7, NEJM 2011

Side effects Pertuzumab

Skin rash

Pertuzumab is associated with a significant risk of rash, and the incidence varies among different tumor types. Prevention, early recognition, and appropriate treatment of this rash may lead to improvement in patient quality of life, adherence to therapy, and possibly optimize clinical outcomes.

Drucker AM, Wu S, Dang CT, Lacouture ME. Risk of rash with the anti-HER2 dimerization antibody pertuzumab: a meta-analysis. Breast Cancer Res Treat. 2012 Sep;135(2):347-54.

Paclitaxel + trastuzumab + pertuzumab (LoE 5D AGO+/-)

1st-Line chemotherapy* + trastuzumab (LoE 1bB AGO+)

(*taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel)

Andersson M., Lidbrink E, Bjerre K. et al.: Phase III Randomized Study Comparing Docetaxel Plus Trastuzumab With Vinorelbine Plus Trastuzumab As First-Line Therapy of Metastatic or Locally Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: The HERNATA Study. DOI: 10.1200/JCO.2010.30.8213

Valero V., Forbes J., Pegramet M. D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-Gene-

Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. DOI: 10.1200/JCO.2010.28.6450

Dawood S., Broglio K., Buzdaret AU. al.: Prognosis of Women With Metastatic Breast Cancer by HER2 Status and Trastuzumab Treatment: An Institutional-Based Review. DOI: 10.1200/JCO.2008.19.9844

Robert N., Leyland-Jones B., Asmaret L. al.: Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel in Women With HER-2–Overexpressing Metastatic Breast Cancer. DOI: 10.1200/JCO.2005.04.1764

Wardley AM., Pivot X., Morales-Vasquez F. et al.: Randomized Phase II Trial of First-Line Trastuzumab Plus Docetaxel and Capecitabine Compared With Trastuzumab Plus Docetaxel in HER2-Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2008.21.6531

Trastuzumab mono (LoE 2bB AGO+/-)

Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-48.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.

Taxanes+ lapatinib (LoE 1b^aA AGO+/-)

Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: a phase III randomized, double-blind study of 580 patients. J Clin Oncol. (2007 ASCO Annual Meeting Proceedings Part I) (2007) 25(18S):1011.

Gelmon KA, Boyle F, Kaufman B, Hunstman D et al. (2012) Open-Label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: Interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. J Clin Oncol 30 (suppl, abstr LBA671), 2012
ember 7, NEJM 2011

Trastuzumab + aromatase inhibitors (if ER+) (LoE 2bB AGO+/-)

Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Revil C, Jones A: Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM Study. *J Clin Oncol* 2009;27:5529–37

Lapatinib + aromatase inhibitors (if ER+) (LoE 2bB AGO+/-)

Johnston S, Pippen Jr J, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S, Pegram M: Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2009.23.3734

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab) **(16/20)**

Further information and references:

Baselga et al., December 7, NEJM 2011

2013

Capecitabine + lapatinib (LoE 1b B AGO+)

Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Grusfeld A, Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, Gorbounova V, Raats JJ, Skarlos D, Newstat B, Roychowdhury D, Paoletti P, Oliva C, Rubin S, Stein S, Geyer CE. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008 Dec;112(3):533-43.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med (2006) 355(26):2733–2743.

When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.

Delea TE, Tappenden P, Sofrygin O, Browning D, Amonkar MM, Karnon J, Walker MD, Cameron D. Cost-effectiveness of lapatinib plus capecitabine in women with HER2+ metastatic breast cancer who have received prior therapy with trastuzumab. Eur J Health Econ. 2012 Oct;13(5):589-603.

Trastuzumab + lapatinib (if CT not possible) (LoE 3b B AGO+)

Trastuzumab plus lapatinib vs lapatinib

Met-HER2posBC phase iii (2nd and further lines; n=291, HR-PFS =0.74, p=0.011; HR OS =0.74, p=0.026)

Blackwell KL, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, Ellis C, Florance A, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Overall survival benefit with lapatinib in combination with trastuzumab for patients with

human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92.

O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. J Clin Oncol 26: 2008 (May 20 suppl; abstr 1015).

TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression) (LoE 2b D AGO +)

Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). J Clin Oncol 26: 2008 (May 20 suppl; abstr 1025).

Review

“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

Pegram M, Liao J. Trastuzumab treatment in multiple lines: current data and future directions. Clin Breast Cancer. 2012 Feb;12(1):10-8.

Taxane + trastuzumab + pertuzumab (LoE 5 D AGO +)

Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab (LoE 5 D AGO +/-)

Trastuzumab mono (DATEN?) (LoE 2b B AGO +/-)

2nd line:

Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-48.

(1st line:

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.)

Trastuzumab + aromatase inhibitors (if ER+)(LoE 3b B AGO +)

Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, Revil C, Jones A: Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM Study. J Clin Oncol 2009;27:5529–37

Lapatinib + aromatase inhibitors (if ER+)(LoE 3b B AGO +)

Johnston S, Pippen Jr J, Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, Press MF, Maltzman J, Florance A, O'Rourke L, Oliva C, Stein S, Pegram M: Lapatinib Combined With Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2009.23.3734

Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (17/20)

Further information and references:

2013

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel) (LoE 5 D AGO +/-)

Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). J Clin Oncol 26: 2008 (May 20 suppl; abstr 1025).

Baselga, J. et al. (2010) Phase II trial of Pertuzumab and Trastuzumab in patients with human epidermal growth factor receptor 2 – positive metastatic breast cancer that progressed during prior Trastuzumab therapy. JCO 28, 1138-1144
Review

“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

Pegram M, Liao J. Trastuzumab treatment in multiple lines: current data and future directions. Clin Breast Cancer. 2012 Feb;12(1):10-8.

Capecitabine + lapatinib (LoE 2b B AGO +)

Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Grusfeld A, Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, Gorbounova V, Raats JJ, Skarlos D, Newstat B, Roychowdhury D, Paoletti P, Oliva C, Rubin S, Stein S, Geyer CE. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat. 2008 Dec;112(3):533-43.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med (2006) 355(26):2733–2743.

Trastuzumab + lapatinib (if CT not possible) (LoE 3bB AGO +)

Blackwell KL, Burstein HJ, Sledge GW, Stein S, Ellis C, Casey M, Baselga J, O'Shaughnessy J; Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy. JCO 2010, 28: 1124-1130

O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. J Clin Oncol 26: 2008 (May 20 suppl; abstr 1015).

Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1) (LoE 5D AGO +)

EMILIA

Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in

HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012

Sachdev JC, Jahanzeb M. Blockade of the HER family of receptors in the treatment of HER2-positive metastatic breast cancer. Clin Breast Cancer. 2012 Feb;12(1):19-29.

Baselga et al., Dec

Trastuzumab in HER2-positive Metastatic Breast Cancer (18/20)

Further information and references:

Registered in HER-2 positive disease (Dosage / Duration):

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.

Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005;23:4265–4274.

Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639-48.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719-26.

Burris H, Yardley D, Jones S, et al. Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer. J Clin Oncol 2004; 22:1621-9.

Dosage:

Baselga J, Carbonell X, Castaneda-Soto NJ, et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. J Clin Oncol 2005;23: 2162-71.

Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol 2003;21:3965-71.

Dawood SS, Kristine B, Hortobagyi GN, Giordano SH. Prognosis of women with stage IV breast cancer by HER2 status and trastuzumab treatment: An institutional based review. J Clin Oncol 26: 2008 (May 20 suppl; abstr 1018).

Bontenbal M, Seynaeve C, Stouthard J, et al. Randomized study comparing efficacy/toxicity of monotherapy trastuzumab followed by monotherapy docetaxel at progression, and combination trastuzumab/docetaxel as first-line chemotherapy in HER2-neu positive, metastatic breast cancer (MBC) (HERTAX study). J Clin Oncol 26: 2008 (May 20 suppl; abstr 1014).

Duration of treatment:

Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). J Clin Oncol 26: 2008 (May 20 suppl; abstr 1025).

2013

Trastuzumab treatment beyond progression

Review

“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

Pegram M, Liao J. Trastuzumab treatment in multiple lines: current data and future directions. Clin Breast Cancer. 2012 Feb;12(1):10-8.

Lapatinib in HER2-positive Metastatic Breast Cancer (19/20)

Further information and references:

Anthracycline and Taxane and Trastuzumab pre-treatment

Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Grusfeld A, Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, Gorbounova V, Raats JJ, Skarlos D, Newstat B, Roychowdhury D, Paoletti P, Oliva C, Rubin S, Stein S, Geyer CE. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat.* 2008 Dec;112(3):533-43.

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Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1025).

O'Shaughnessy J, Blackwell KL, Burstein H, et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 1015).

Blackwell KL, Burstein HJ, Sledge GW, Stein S, Ellis C, Casey M, Baselga J, O'Shaughnessy J; Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy. *JCO* 2010, 28: 1124-1130

Trastuzumab naive patients: first line therapy

Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: a phase III randomized, double-blind study of 580 patients. *J Clin Oncol.* (2007 ASCO Annual Meeting Proceedings Part I) (2007) 25(18S):1011.

Brain metastases (radioresistance)

Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2008;26:1993-9.

Palliative High Dose Chemotherapy (20/20)

Further information and references:

A recent Cochrane systematic review on six randomised controlled trials and 850 patients found an increase in treatment-related deaths among the high dose group compared to the control (conventional dose) group (RR 4.07 (95% CI 1.39, 11.88)). There was no statistically significant difference in overall survival between the high dose and control groups at one year, three years or five years. At one and five years of follow up, there was a statistically significant difference in event-free survival, favouring the high dose group (one year: RR 1.76 (95% CI 1.40, 2.21); five years: RR 2.84 (95% CI 1.07, 7.50)). Toxicity was more severe in the high dose group. Only one of the trials has followed up all women for five years and further data are awaited. Although there is statistically significant evidence that high dose chemotherapy and autograft improves event free survival compared to conventional chemotherapy, the authors of this report conclude that high dose chemotherapy with bone marrow or stem cell transplantation should not be given to women with metastatic breast cancer outside of clinical trials.

This conclusion remains valid, if more recent published trials are also taken into consideration.

Farquhar C, Marjoribanks J, Bassier R, Hetrick S, Lethaby A. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003142.

Vredenburgh JJ et al., Bone Marrow Transplantation, 37:985-7 (2006)

Biron P et al., Bone Marrow Transplantation, Epub 11/2007

Tailored therapy in MBC

Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.

Hatschek T, Carlsson L, Einbeigi Z, Lidbrink E, Linderholm B, Lindh B, Loman N, Malmberg M, Rotstein S, Söderberg M, Sundquist M, Walz TM, Hellström M, Svensson H, Aström G, Brandberg Y, Carstensen J, Fernö M, Bergh J. Individually tailored treatment with epirubicin and paclitaxel with or without capecitabine as first-line chemotherapy in metastatic breast cancer: a randomized multicenter trial. *Breast Cancer Res Treat.* 2012 Feb;131(3):939-47.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Osteooncology and Bone Health

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Bisphosphonates in Breast Cancer

Oxford / AGO LoE / GR

- | | | | |
|--|-----------|----------|------------|
| ➤ Hypercalcemia | 1a | A | ++ |
| ➤ Reduction of skeletal events (complications) | 1a | A | ++ |
| ➤ Reduction of bone pain | 1a | A | ++ |
| ➤ Treatment beyond progression of bone met's | 5 | D | ++ |
| ➤ In combination with neoadjuvant chemotherapy | 2b | C | +/- |
| ➤ Prevention of bone metastases/ survival advantage | | | |
| ➤ Adjuvant in postmenopausal patients | 1a | A | + |
| ➤ Advanced breast cancer | 2b | C | +/- |
| ➤ Prevention of breast cancer with oral BPs (in women receiving BP for low BMD) | 3b | C | +/- |

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Denosumab in Breast Cancer

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- **Reduction of hypercalcemia** **2a A ++**
- **Reduction of skeletal complications** **1a A ++**
- **Reduction of bone pain** **1b B ++**
 - **Increasing bone pain-free survival** **1b A ++**
- **Treatment beyond progression** **5 D +**
 - **Progression under bisphosphonates** **4 C +/-**

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Bone Modifying Agents for the Therapy of Bone Metastases

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| | | | |
|--|----|---|----|
| ➤ Clodronate PO 1600 mg daily | 1a | A | ++ |
| ➤ Clodronate IV 1500 mg q3w / q4w | 1a | A | ++ |
| ➤ Pamidronate IV 90 mg q3w / q4w | 1a | A | ++ |
| ➤ Ibandronate IV 6 mg q3w / q4w | 1a | A | ++ |
| ➤ Ibandronate PO 50 mg daily | 1a | A | ++ |
| ➤ Zoledronate IV 4 mg q4w | 1a | A | ++ |
| ➤ Denosumab 120 mg s.c. q4w | 1a | A | ++ |
| ➤ Other doses or schedules, e.g. derived from studies of adjuvant therapy or therapy of osteoporosis | 5 | D | -- |

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Skeletal Metastasis

Treatment with Radionuclids

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- **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain**

(prerequisite: hot spots in the bone scintigraphy)

- **^{186}Re -hydroxyethylidene-diphosphonat (e.g. ^{186}Re -HEDP)**

1b B +

- **^{153}Sm**

2b B +

- **^{89}Sr (e.g. Sr^{89})**

1b B +

- **^{223}Ra**

1b C +

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.

Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b

GR: C

AGO: ++

- **Spinal cord compression**
 - **With progressive neurological symptoms**
 - **With pathological fractures**
- **Instability of the spine**
- **Lesions in pre-irradiated parts of the spine**

Bone Metastases

Acute Spinal Cord Compression / Paraplegia

Oxford / AGO
LoE / GR

- **Decompression surgery, reduction of tumor volume, stabilisation surgery (< 24 h) and irradiation of the spine (RT)** **2b C ++**
- **Irradiation of the spine (< 24 h) +/- steroids** **3b C ++**
- **Immediate start of treatment** **1c D ++**

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Clinical trials have included patients with different tumor entities!

Surgery for Bone Metastases

Spine and limbs

Oxford LoE: 3b

GR: C

AGO: +

- **Marrow splints**
- **Osteosynthesis**
- **Bone replacement by PMMA or titanspacer**
- **Tumor-Endoprothesis**
- **Vertebroplasty / Kyphoplasty**
- **Kypho-IORT (only in studies)***
- **Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)**

***Study participation recommended**

Metastatic Bone Disease: Radiotherapy

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Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
 - Single RT = fractionated RT
- With neuropathic bone pain
- Asymptomatic isolated bone metastases

Oxford / AGO LoE / GR

1a B ++

1a B ++

1a B ++

2a B ++

1b B ++

5 D +/-

Only few studies included breast cancer patients!

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Metastatic Bone Disease

Recurrent Bone Pain

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Recurrent bone pain in pre-irradiated parts of the skeleton

- | | | | |
|------------------------------|----|---|----|
| ➤ Single RT (1 x 8 Gy) | 3b | C | ++ |
| ➤ Fractionated RT (6 x 4 Gy) | 3b | C | + |
| ➤ Radionuclid therapy | 3b | C | + |

Further
Information

References

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

**Oxford
LoE**

- | | |
|---|-----------|
| ➤ Renal function deterioration due to IV-aminobisphosphonates | 1b |
| ➤ Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.8% / 1.8%) | 1b |
| ➤ Association with anti-angiogenetic therapies | 3b |
| ➤ Severe hypocalcemia (Dmab>BPs) | 1b |
| ➤ Acute phase reaction (IV Amino-BPs, Db) 10-30% | 1b |
| ➤ Gastrointestinal side effects (oral BPs) 2-10% | 1b |

**In adjuvant bisphosphonate therapy,
major side effects were rarely observed (except APR).**

Recommendations for Precautions to Prevent ONJ*

Oxford LoE: 4

GR: C

AGO: +

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (**LoE 2b**)
- Optimize dental status before start of bisphosphonate or denosumab treatment, if feasible (**LoE 2b**)
- Inform patients about ONJ risk and educate about early symptom reporting
- In case of high risk for ONJ, use oral bisphosphonate

In adjuvant bisphosphonate therapy, ONJ was rare

***Osteonecrosis of the jaw**

Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage

Oxford / AGO
LoE / GR

- **Clodronate (oral)**
 - Postmenopausal patients
 - Premenopausal patients

- **Aminobisphosphonates (iv or oral)**
 - Postmenopausal patients
 - Premenopausal patients

1a A +
1a B +/-

1a A +
1a B +/-

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- **Coleman R, Gnant M, Paterson A et al. Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer. A meta-analysis of individual patients data from randomized trials. SABCS 2013, abstract S4-07**
- **Winter MC, Coleman RE. Bisphosphonates in the adjuvant treatment of breast cancer: an Overview. Clin Oncol 2013;25:135-45**
- **Zhu J, Zheng Y, Zhou Z. Oral adjuvant clodronate therapy could improve overall survival in early breast cancer. Results from an updated systematic review and meta-analysis. Eur J Cancer 2013 ;49:2086-92**
- **He M, Fan W, Zhang X. Adjuvant zoledronic acid therapy for patients with early stage breast cancer: an updated systematic review and meta-analysis. J Hematol Oncol 2013, 6:80: <http://www.jhoonline.org/content/6/1/80>**
- **Valachis A, Polyzos NP, Coleman RE et al. Adjuvant therapy with zoledronic acid in patients with breast cancer. A systematic review and meta-analysis. The Oncologist 2013;18:353-61**
- **Figuerola-Magalhães, Miller RS. Bone-Modifying Agents as Adjuvant Therapy for early-stage breast cancer. Oncology 2012;26: <http://www.cancernetwork.com/breast-cancer/content/article/10165/2107660>**
- **Yan T, Yin W, Zhou Q et al. The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials. Eur J Cancer 2012; 48:187-95**
- **Chlebowski RT, Col N. Bisphosphonates and breast cancer, incidence and recurrence. Breast Disease 2011;33:83-101**

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Dosage of Adjuvant Bisphosphonates for Improvement of Survival

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➤ Non-Aminobisphosphonates:

➤ **Clodronate PO 1600mg/d (Bonefos/ Clodronic acid)**

➤ **Clodronate PO 1040mg/d (Ostac)**

➤ Aminobisphosphonates:

➤ **Zoledronate IV 4mg/6m (Zometa/ Zoledronic acid)**

➤ **Ibandronate PO 50mg/d (Bondronat/ Ibandronic acid)**

➤ **Pamidronate PO (orally not available in most countries)**

➤ **Risedronate PO 35mg/w (Actonel/ Risedronic acid)**

➤ **Alendronate PO 70mg/w (Fosamax/ Alendronic acid)**

Aminobisphosphonates include:

Zoledronic acid (65%), Oral ibandronate (24%), Oral pamidronate (8%),
Oral residronate (2%), Oral alendronate (1%) (data from EBCTCG-metaanalysis)

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Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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LoE / GR**

➤ **Bisphosphonates**

➤ **Therapy**

1b B ++

➤ **Prevention**

1b A +

Denosumab

➤ **Therapy**

1b B ++

➤ **Prevention**

1b A +

➤ **HRT (independent from ER-status of BC)**

5 D -

➤ **Regular BMD-measurement recommended (Intervals depending from previous T-values)**

2b B +

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

**Oxford / AGO
LoE / GR**

- | | | | |
|---|----|---|----|
| ➤ Physical activity | 4 | C | ++ |
| ➤ Avoiding immobilisation | 4 | C | ++ |
| ➤ Calcium (1000–1500 mg/d. Nutrit./Suppl.)** | 4 | C | ++ |
| ➤ Vitamine D suppl. (800–2000 U/d) | 4 | C | ++ |
| ➤ Reduction of smoking | 4 | C | ++ |
| ➤ Avoiding BMI < 20 mg/m ² | 3b | C | ++ |
| ➤ Drugs approved for the treatment of osteoporosis in adults (see next slide) | | | |

*http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2009
New DVO-guidelines will be presented soon in 2014

**if intestinal uptake is reduced (in combination with Vit D only)

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References

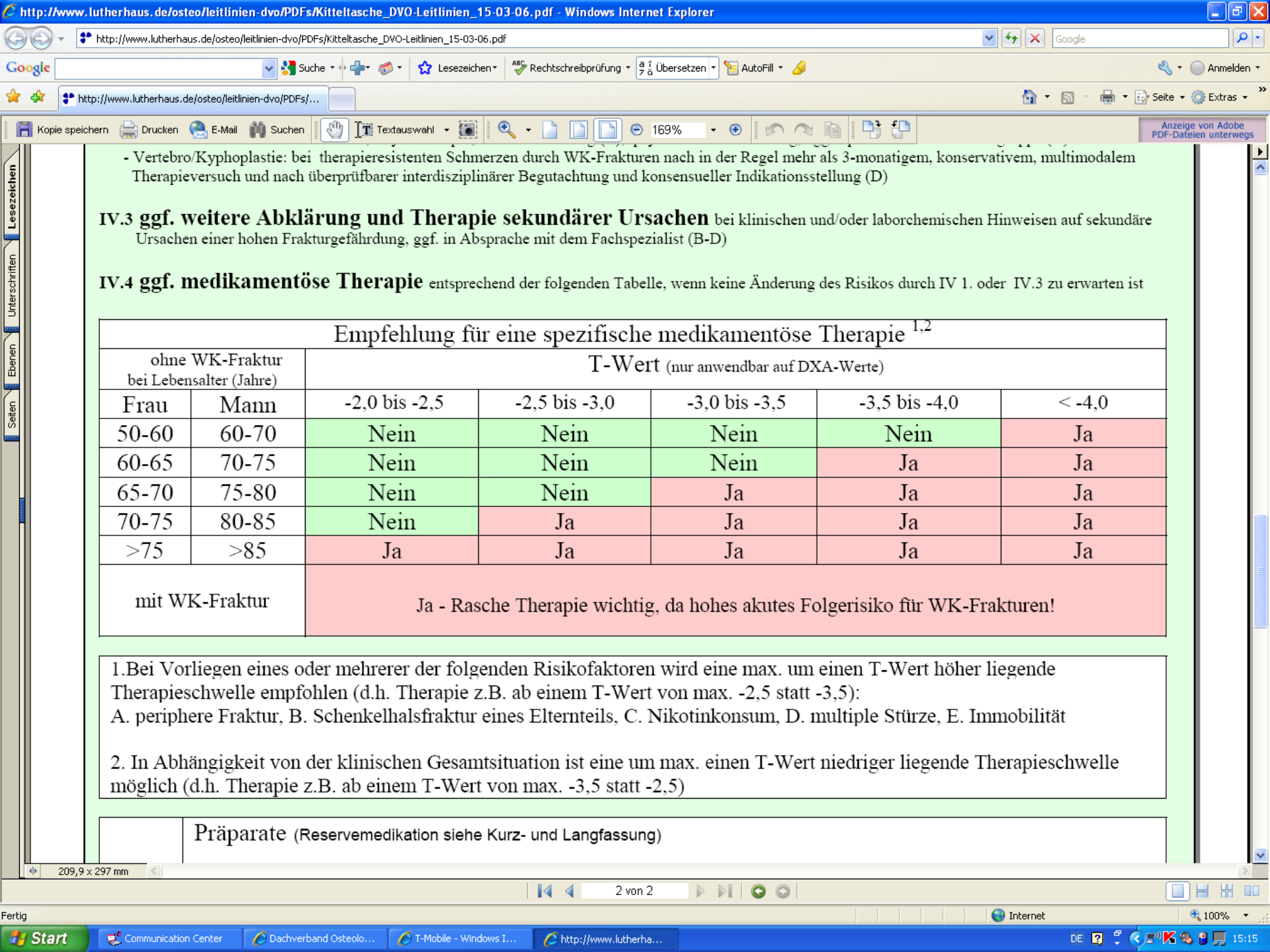
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Medical Treatment of Osteoporosis

Oxford / AGO LoE / GR

| | | | | |
|---|---|-----------|----------|-----------|
| ➤ | Alendronate 70 mg po/w* | 1b | B | ++ |
| ➤ | Denosumab 60 mg sc/6m* | 1b | B | ++ |
| ➤ | Ibandronate 150 mg po/m* | 1b | B | ++ |
| ➤ | Ibandronate 3 mg iv/3m | 1b | B | + |
| ➤ | Parathyroid hormone (1-84) 100 µg sc/d | 1b | B | + |
| ➤ | Raloxifene 60 mg po/d | 1b | B | + |
| ➤ | Risedronate 35 mg po/w* | 1b | B | ++ |
| ➤ | Strontium ranelate 2 g po/d | 1b | B | + |
| ➤ | Teriparatide (1-34) 20 µg sc/d | 1b | B | + |
| ➤ | Zoledronate 5 mg iv/12 m* | 1b | B | ++ |

* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis



- Vertebro/Kyphoplastie: bei therapieresistenten Schmerzen durch WK-Frakturen nach in der Regel mehr als 3-monatigem, konservativem, multimodalem Therapieversuch und nach überprüfbarer interdisziplinärer Begutachtung und konsensueller Indikationsstellung (D)

IV.3 ggf. weitere Abklärung und Therapie sekundärer Ursachen bei klinischen und/oder laborchemischen Hinweisen auf sekundäre Ursachen einer hohen Frakturgefährdung, ggf. in Absprache mit dem Fachspezialist (B-D)

IV.4 ggf. medikamentöse Therapie entsprechend der folgenden Tabelle, wenn keine Änderung des Risikos durch IV 1. oder IV.3 zu erwarten ist

| Empfehlung für eine spezifische medikamentöse Therapie ^{1,2} | | | | | | |
|---|-------|---|---------------|---------------|---------------|--------|
| ohne WK-Fraktur bei Lebensalter (Jahre) | | T-Wert (nur anwendbar auf DXA-Werte) | | | | |
| Frau | Mann | -2,0 bis -2,5 | -2,5 bis -3,0 | -3,0 bis -3,5 | -3,5 bis -4,0 | < -4,0 |
| 50-60 | 60-70 | Nein | Nein | Nein | Nein | Ja |
| 60-65 | 70-75 | Nein | Nein | Nein | Ja | Ja |
| 65-70 | 75-80 | Nein | Nein | Ja | Ja | Ja |
| 70-75 | 80-85 | Nein | Ja | Ja | Ja | Ja |
| >75 | >85 | Ja | Ja | Ja | Ja | Ja |
| mit WK-Fraktur | | Ja - Rasche Therapie wichtig, da hohes akutes Folgerisiko für WK-Frakturen! | | | | |

1. Bei Vorliegen eines oder mehrerer der folgenden Risikofaktoren wird eine max. um einen T-Wert höher liegende Therapieschwelle empfohlen (d.h. Therapie z.B. ab einem T-Wert von max. -2,5 statt -3,5):
A. periphere Fraktur, B. Schenkelhalsfraktur eines Elternteils, C. Nikotinkonsum, D. multiple Stürze, E. Immobilität

2. In Abhängigkeit von der klinischen Gesamtsituation ist eine um max. einen T-Wert niedriger liegende Therapieschwelle möglich (d.h. Therapie z.B. ab einem T-Wert von max. -3,5 statt -2,5)

Präparate (Reservemedikation siehe Kurz- und Langfassung)

Therapieempfehlung für Personen ohne spezifische Risiken und/oder Frakturen

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in der DGOG e. V.
sowie
in der DKG e. V.

Guidelines Breast
Version 2014.1

Schwellenwerte der T-Werte der Knochendichte für eine medikamentöse Therapie in Abhängigkeit vom Geschlecht und dem Lebensalter für Personen ohne prävalente Frakturen oder andere spezifische Frakturrisiken

Lebensalter in Jahren T-Wert

| Frau | Mann | T-Wert |
|-------|-------|--------|
| <50 | <60 | −4,0 |
| 50–60 | 60–70 | −4,0 |
| 60–65 | 70–75 | −3,5 |
| 65–70 | 75–80 | −3,0 |
| 70–75 | 80–85 | −2,5 |
| >75 | >85 | −2,0 |

www.ago-online.de

Further
Information

References

FORSCHEN
LEHREN
HEILEN

http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2009
Neue DVO-Leitlinie erscheint voraussichtlich 2014

Therapieempfehlung für Personen mit spezifische Risiken und/oder Frakturen

Risikofaktoren, die die Therapieschwelle mitbestimmen (auszugsweise*)

1. Allgemeine Risiken

| | |
|--|---|
| periphere Fraktur nach dem 50. Lebensjahr | B |
| multiple Stürze | B |
| Immobilität | B |
| fortgesetzter Nikotinkonsum | B |
| Abnahme der DXA-Knochendichte am Gesamtfemur um 5% und mehr in 2 Jahren | B |
| Hypogonadismus | B |

2. Krankheiten

| | |
|-------------------------|---|
| Diabetes mellitus Typ 1 | B |
| rheumatoide Arthritis | D |

3. Medikamente

| | |
|--|---|
| Antiandrogene/ Antiöstrogene Therapie | B |
| Aromatasehemmer-Therapie | D |
| orale Glukokortikoide < 7,5 mg für mehr als 3 Monate | B |

*http://www.dv-osteologie.org/dvo_leitlinien/dvo-leitlinie-2009

Neue DVO-Leitlinie erscheint vermutlich 2014

Osteooncology and Bone Health (2/22)

No further information

No references

Bisphosphonates in Breast Cancer (3/22)

No further information

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Denosumab in Breast Cancer (4/22)

No further information

No references

Bone Modifying Agents for the Therapy of Bone Metastases (5/22)

No further information

No references

Skeletal Metastasis Treatment with Radionuclids (6/22)

Further information:

Bei multilokaler Schmerzsymptomatik aufgrund einer kleinherdigen disseminierten ossären Metastasierung stellt die Therapie mit osteotropen Radionukliden eine zusätzliche Option im multimodalen analgetischen Therapiekonzept dar. Sie kann angewendet werden, wenn durch eine zuvor erforderliche diagnostische Skelettszintigraphie mit ^{99m}Tc eine ausreichend hohe Affinität in befallenen Knochenabschnitten dokumentiert ist, keine pathologische Fraktur vorliegt und die Hämatopoese nicht (z.B. durch eine Karzinose oder myelotoxische Chemotherapie) eingeschränkt ist. Der Effekt der Radionuklidtherapie ist dabei weniger von der Histologie, sondern vor allem vom pathologisch gesteigerten Knochenstoffwechsel abhängig. Verwendet werden heutzutage vor allem die Radiopharmaka ¹⁵³Sm (Sm-EDTMP), ⁸⁹Sr (Sr-Chlorid) und ¹⁸⁶Re (Re-HEDP). Sie unterscheiden sich in ihrer Reichweite, physikalischen Halbwertszeit und Energiedosisleistung, die maßgeblich sind für deren therapieassoziierte Nebenwirkungen. Die Ansprechraten liegen zwischen 70 und 90 % mit kompletter Schmerzfreiheit bei 20-30%. Die Anzahl der in Studien zur Schmerzbeeinflussung ossärer Metastasen von Mammakarzinomen mit Radionukliden untersuchten Patientinnen ist jedoch relativ klein. Der maximale analgetische Effekt wird nach etwa 10 Tagen erreicht und hält – abhängig vom eingesetzten Radiopharmakon – im Mittel 5 bis 8 Wochen an.

Vorteile gegenüber der lokalen perkutanen Radiotherapie bestehen in der Möglichkeit von Wiederholungsbehandlungen und der Beeinflussung bereits anreichernder, aber noch nicht symptomatischer Metastasen. Einschränkungen der Radionuklidtherapie sind begründet in deren z.T. ausgeprägter, jedoch zumeist reversiblen Myelosuppression bei 20-60% der Patientinnen und die Beschränkung der Therapie auf kleinherdige Knochenmetastasen aufgrund der begrenzten Reichweite der hierbei emittierten β -Strahlung. Sie ist nicht geeignet bei größeren Knochenmetastasen oder begleitenden Weichteiltumoren.

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Metastatic Bone Disease of the Spine (7/22)

Further information:

Bei Wirbelsäuleninstabilität, ossärer Kompression und/oder Paraplegie stellt die operative Intervention mit anschließender Radiotherapie das mit hoher Evidenz belegte geeignetste Vorgehen dar. Bei subklinischer Rückenmarkkompression, d.h. bei nicht paraplegischen und ambulant zu behandelnden Patientinnen ohne Anhalt für Instabilität, ist die Radiotherapie als Therapie der Wahl gut validiert. In dieser Situation kann auf eine begleitende Kortisontherapie verzichtet werden. Wenn bei ossären Wirbelsäulenmetastasen mit konsekutiver Spinalkanalbeteiligung Kortikoide eingesetzt werden, ist der Nutzen nur für eine hochdosierte Dexamethason-Medikation (96 mg/d) gut belegt.

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Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/22)

Further information:

Metastatic spinal cord compression (MSCC) as well as bone metastases should be managed in an interdisciplinary approach mostly as combined modality treatment according to the specific clinical situation. Best results are achieved by close interdisciplinary cooperation minimizing the interval between diagnosis and onset of treatment. Most important criteria for prognosis and choice of treatment (mostly combined multimodal therapy) are neurological status at diagnosis of MSCC, time course of duration and progression of the neurological symptoms. RT is effective and regarded as treatment of choice for MSCC with or without motor deficits and / or bone metastases, which do not need immediate surgical intervention. It may be used either postoperatively or as primary treatment in case of inoperability. An optimal dose-fractionation schedule or optimal standard dose for treatment of bone metastases has not been established. With regard to different therapeutic goals, different dose concepts and fractionation schedules, single versus multifraction palliative RT (1 x 8, 5 x 4, 10 x 3, 15 x 2.5, 20 x 2 Gy), should be adapted individually.

The role of radiotherapy is well established in the case of MSCC without neurological deficits. Additionally, primary radiotherapy is indicated in the case of beginning paraplegia with complete response to steroids and lack of necessity to operate. Radiotherapy is the method of choice in inoperable cases due to low rate of side effects, short hospitalisation / outpatient procedure and – a key factor – the radiosensitivity of breast cancer. These advantages are also relevant in patients with a dismal overall prognosis, short life expectancy and severe co-morbidity, especially because radiotherapy is equivalent to simple laminectomy with respect to the functional outcome. Local radiotherapy is indicated postoperatively to achieve local tumour control and should be initiated as soon as possible (LoE IIa, grade of recommendation A).

3D conformal radiotherapy or intensity modulated radiotherapy (IMRT) allows concave shaping of isodose distributions with at least partial sparing of critical structures adjacent to the target volume (14, 25, 65). Thus, the maximal and mean doses to the spinal cord can be kept below 20% and 50% respectively of the dose given to the vertebral body.

In case of in-field recurrence of MSCC, re-irradiation can be performed in selected cases, again considering individual factors and therapeutic aims (LoE III). In these situations all technical efforts should be used to limit the dose to the spinal cord.

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Bei beginnender Querschnittsymptomatik infolge metastatischer Rückenmarkskompression ist eine operative Entlastung (z.B. Laminektomie) so früh als möglich anzustreben, um notfallmäßig durch die operativ-mechanische Dekompression eine spinale Entlastung zu erreichen. Die operative Entlastung sollte innerhalb kürzester Zeit (Stunden!) erfolgen, was ggf. auch für die Radiotherapie gilt: Notfallbehandlung innerhalb von 24 Stunden! In allen operierten Fällen ist eine lokale Nachbestrahlung erforderlich, um eine lokale Tumor- und Metastasenkontrolle zu erreichen. Das Ausmaß der Rückbildung von spinalen Symptomen ist maßgeblich vom Zeitintervall zwischen dem Einsetzen der Symptome und dem Beginn der Radiotherapie sowie vom prätherapeutisch bestehendem Mobilitätsgrad der Patientin abhängig.

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Surgery for Bone Metastases (9/22)

Further information:

Osteosynthesen und/oder Einbringung von Polymethylmethacrylat (PMMA; Knochenzement) sind operative Standardverfahren zur Behandlung metastatisch bedingter pathologischer Frakturen. Mit diesen können eine rasche Wiederherstellung bzw. Verbesserung frakturbedingter Funktionsstörungen und Schmerzlinderungen erreicht werden. Eine prophylaktische operative Fixierung von drohenden Frakturen infolge einer Metastasierung ist an statisch belasteten langen Röhrenknochen zu erwägen, wenn keine Konsolidierung durch Radio-, systemische antineoplastische oder Bisphosphonattherapie erreicht wird. Zur Abschätzung des individuellen Risikos von Frakturen und somit zur Entscheidung über eine prophylaktische operative Intervention können unterschiedliche Risikoscores hilfreich sein.

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Metastatic Bone Disease: Radiotherapy (10/22)

Further information:

Bone metastases in breast cancer have a high clinical relevance and are commonly seen by the radiation oncologist. Different therapeutic goals (pain relief, local tumour control, prevention or improvement of motor deficits, stabilization of the spine or other bones) require complex approaches considering individual factors (i.e. life expectancy, tumour progression at other sites). Best results are achieved by close interdisciplinary cooperation minimizing the interval between diagnosis and onset of treatment. Most important criteria for prognosis and choice of treatment (mostly combined multimodal therapy) are neurological status at diagnosis of MSCC, time course of duration and progression of the neurological symptoms. RT is effective and regarded as treatment of choice for MSCC with or without motor deficits and / or bone metastases, which do not need immediate surgical intervention. It may be used either postoperatively or as primary treatment in case of inoperability. An optimal dose-fractionation schedule or optimal standard dose for treatment of bone metastases has not been established. With regard to different therapeutic goals, different dose concepts and fractionation schedules, single versus multifraction palliative RT (1 x 8, 5 x 4, 10 x 3, 15 x 2.5, 20 x 2 Gy), should be adapted individually.

The principles of therapy and the guidelines for palliative radiotherapy of bone metastases in patients with breast cancer might be summarized regarding different therapeutic goals:

Therapeutic goal: pain reduction: Single dose RT 1 x 8 Gy (cave: >8 Gy to the myelon may cause paresis) (LoE III)

Therapeutic goal: stabilisation, good prognosis: Fractionated regimen preferable e.g. 10-12 x 3 Gy (LoE IIb)

Oligometastases: Full dose fractionated regimen recommended, e.g.. 20-25 x 2 Gy to 40-50 Gy (LoE IIb, III)

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Metastatic Bone Disease Recurrent Bone Pain (11/22)

Further information:

Indication and dosage of an optional re-irradiation depend on the previously applied dose, the initial response, the interval to the preceding radiation therapy, and the dose per fraction to critical organs. A re-irradiation of metastases in the extremities or the peripheral parts of the trunk is usually possible. In most cases one may again apply full doses, e.g. 10 x 3 Gy or 20 x 2 Gy, favouring the use of small single doses.

Prior to re-irradiation of the base of skull, the vertebral column and the pelvic bones overall radiation tolerance of the critical organs like brain stem, spinal cord, bowel and bladder has to be considered. Following a typical first course of 10 x 3 Gy without hot spots in the brain stem or the spinal cord, a partial recovery after about 6 months may be assumed.

Therefore, a second course of radiotherapy can be performed in urgent cases with an increased but acceptable risk by applying doses of up to 15 x 2 Gy, provided that tolerance doses of the critical organs are respected.

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Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/22)

No further information

No references

Recommendations for Precautions to Prevent ONJ* (13/22)

No further information

No references

Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (14/22)

No further information

No references

Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (15/22)

No further information

No references

Dosage of Adjuvant Bisphosphonates for Improvement of Survival (16/22)

No further information

No references

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/22)

No further information

No references

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (18/22)

No further information

No references

Medical Treatment of Osteoporosis (19/22)

No further information

No references

(20/22)

No further information

No references

Therapieempfehlungen für Personen ohne spezifische Risiken und/oder Frakturen (21/22)

No further information

No references

Therapieempfehlungen für Personen mit spezifischen Risiken und/oder Frakturen (22/22)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Specific Sites of Metastases

Specific Sites Of Metastases

Local Approaches to Metastatic Disease

- **Version 2002:**
Dall / Fersis / Friedrich
- **Versions 2003–2013:**
**Bauerfeind / Bischoff / Böhme / Brunnert / Diel
/ Friedrich / Friedrichs / Gerber / Hanf / Janni /
Lück / Maass / Oberhoff / Rezai / Schaller /
Seegenschmiedt / Solomayer / Souchon**
- **Version 2014:**
Fehm / Gerber

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Specific Sites of Metastases

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- **Liver and lung metastases**
- **Malignant pleural and pericardial effusions**
- **Ascites**
- **Bone marrow involvement**
- **Soft tissue metastases**
- **Any other organs**
- **Consider also chapter „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“**

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Further
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General Aspects of Metastases Surgery or Ablation

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- **Histological / cytological verification**
- **Systemic treatment preferred**
- **Consider surgery only in case of good response to palliative treatment**
- **Metastases surgery is an option in good condition pts. with late occurred oligometastases**
- **Surgical treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction**
- **Systemic treatment after surgery**

**Oxford / AGO
LoE / GR**

| | | |
|-----------|----------|------------|
| 3 | B | + |
| 2a | B | ++* |
| 2b | C | + |
| 3 | D | + |
| 5 | D | +/- |
| 5 | D | ++ |

*** See chapters with systemic treatment recommendations**

Further
Information

References

Breast Surgery in Primary Metastatic Disease

Oxford / AGO

LoE / GR

- | | | | |
|---|---|---|-----|
| ➤ Local treatment (R0) of primary tumor | 2 | B | +/- |
| ➤ Axillary surgery for cN1 | 5 | C | +/- |
| ➤ Sentinel in cN0 | 5 | C | - |

Liver Metastasis

Local Therapy

Oxford / AGO
LoE / GR

- | | |
|--|--|
| <p>➤ Resection of liver metastasis (R0)</p> <p>Individual cases (liver function) with resectable metastases</p> <p>HR positive; chemotherapy sensible</p> | <p>3b C +/-</p> |
| <p>➤ Regional chemotherapy</p> | <p>4 C +/-</p> |
| <p>➤ Regional radiotherapy</p> <p>(SIRT, radiochemoembolization, other modalities)</p> | <p>3b C +/-</p> <p>4 C +/-</p> |
| <p>➤ Thermoablation</p> <p>(RFA, LITT, cryotherapy)</p> | <p>3b C +/-</p> |

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Pulmonary Metastases

Local Therapy

Oxford / AGO

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- **VATS or conventional resection** **3b C +/-**
- **Thermoablation (CT-guided RFA, LITT)** **3b C +/-**

Malignant Pleural Effusions (MPE)

Incidence:

- ~ 10 % of all breast cancer patients
- ~ 50% of pat. with advanced breast cancer
- ~ 30% of all MPE are caused by breast cancer

Clinical presentation:

- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic
- Survival is related to the presence of additional metastases, age and extent of involving the pleural surface

Diagnostic procedures:

- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion (cytology, histology by thoracoscopy)

Malignant Pleural Effusion (MPE)

Local Therapy

Oxford / AGO
LoE / GR

- | | | |
|--|-------------|------------|
| ➤ VATS and Talcum-pleurodesis* | 1b B | ++ |
| ➤ Chemical pleurodesis | | |
| ➤ Talcum slurry | 1a B | + |
| ➤ Bleomycin, Doxycycline, Mitoxantrone | 2b C | +/- |
| ➤ Povidone iodide | 3b C | +/- |
| ➤ Continuous pleural drainage | 2a B | + |
| ➤ Systemic treatment after pleurodesis | 3b C | +/- |
| ➤ Local antibody therapy (i.e. Catumaxomab) | 3b C | - |
| ➤ Repeated pleural drainage | 5 D | - |

* Adequate pain-relief

VATS: video-assisted thoracoscopic surgery

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Malignant Ascites

Local Therapy

Treatment according to:

Symptoms

Clinical manifestations

Anticipated response to systemic therapy

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LoE / GR

Ascites:

- | | | | |
|---|----|---|-----|
| ➤ Puncture, drainage | 4 | D | ++ |
| ➤ Local chemotherapy | 3b | D | +/- |
| ➤ Systemic therapy | 3b | D | ++ |
| ➤ Local antibody therapy (i.e. Catumaxomab) | 3b | D | +/- |

Malignant Pericardial Effusion

Local Therapy

Oxford / AGO
LoE / GR

Symptomatic pericardial effusion:

- Drainage, fenestration 3b B ++
- VATS (video-assisted thorac. surgery) 4 D +
- US-guided puncture + instillation of mitoxantron, cisplatin 4 D +/-

Bone Marrow Involvement Associated with Pancytopenia

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LoE / GR

Weekly chemotherapy with*:

**Epirubicin, Doxorubicin, Paclitaxel,
Capecitabine**

4 D ++

HER2 pos.: add anti-HER2 treatment

5 D ++

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Further
Information

References

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* Consider pre-treatment

Soft Tissue Metastasis

Local Therapy

Oxford / AGO

LoE / GR

Radiotherapy (if no immediate surgery is indicated or even after surgery):

- | | |
|------------------------------------|----------------|
| ➤ Paresis, spinal cord compression | 2b C ++ |
| ➤ Plexus infiltration | 3b C ++ |
| ➤ Soft tissue metastasis | 3b C + |

Further
Information

References

Specific Sites of Metastases (2/13)

Further information:

Screened data bases: Pubmed 2005 - 2013, ASCO 2011 – 2013, SABCS 2011 – 2013, Cochrane data base (2013)

Screened guidelines:

NCI (National Cancer Institute , 2013): <http://www.cancer.gov>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2013) <http://www.asco.org>

CMA (Canadian Medical Association , 2013): <http://www.cmaj.ca>

NCCN (National Comprehensive Cancer Network , 2013): <http://www.nccn.org>

No references

Specific Sites Of Metastases (3/13)

Further information:

Specific sites of metastases are liver, lung, pleura, pericard, ascites, bone marrow, soft tissue (muscle, subcutaneous fatty tissue, fascia etc.). Breast cancer metastases in the orbita, adrenals, ovaries, uterus, stomach, colon, gall bladder a.s.o. are very seldom seen clinically. So there are only case reports or series. In such cases treatment options must be discussed individual.

No references

General Aspects of Metastases Surgery or Ablation (4/13)

Further information:

The systemic treatment of metastatic disease is standard. In general surgery of distant metastases of breast cancer should be considered in patients with a good health condition, oligometastases and a long distance between primary treatment and the occurrence of metastases.(1-5). Good response to palliative treatment may also indicate patients who will benefit from breast surgery. Reported improved overall survival might be the result of patients selection. Before surgery is done metastases should be confirmed as such one by histology. By that a secondary malignancy can be excluded. A re-evaluation of receptor- and HER2-status in metastases is mandatory, because a receptor-shift occurs in nearly 20 % with an impact on systemic treatment. Other indications for surgical intervention are symptoms like pain, exulceration or persistence after systemic treatment.

Because no data from prospective studies are available, clinicians must weigh retrospective experiences and clinical judgment in deciding whether to offer surgery or techniques for tumor disturbance to these patients. An ongoing trial, E2108 (<http://clinicaltrials.gov/show/NCT01242800>) has been designed to assess the effect of breast surgery in metastatic patients responding to first-line systemic therapy

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Breast Surgery in Metastatic Disease (5/13)

Further information:

The management of primary stage IV (metachronous or primary metastatic) breast cancer focuses on systemic therapy for distant sites. The impact of local treatment extent on overall survival is still under discussion. However retrospective data on more than 30,000 women from North America and Europe have now been published, showing a robust association between surgery or radiotherapy for the primary tumor and prolonged survival.(1) Many questions remain, most importantly, whether this observed association reflects a selection of women with good prognosis for primary site therapy; others relate to the fraction of women in published studies who were diagnosed with metastatic disease postoperatively, whether specific subsets of metastases and biological subtypes would derive greater benefit, and the appropriate timing and extent of local therapy. Depending on the extent of metastatic disease, a local excision of primary tumor or mastectomy with sufficient health margins is recommended.(2-6) An axillary surgery is only indicated for bulky disease. The impact of local radiotherapy on survival is unknown. It should be mentioned, that there are reports, which could not find an advantage regarding overall survival for local surgery in this situation.

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Liver Metastasis - Local Therapy (6/13)

Further information:

Resection of liver metastases should only be performed if histological verification was done, if R0-resection is feasible and no extrahepatic metastases were present. Other procedures like regional radiotherapy as well as thermoablation are indicated in individual cases. The efficacy of the last ones is primarily determined by preablation tumor size and location in relation to the hilum. There are no data to legitimate a regional chemotherapy of liver alone. Mostly a survival benefit for surgery or other ablation techniques have been reported. However this could be the result of patients selection. Diagnostic laparoscopy in combination with intraoperative ultrasound should be planned in future experience.

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SIRT (selective internal radiation therapy):

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RFA (Radiofrequency ablation):

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Pulmonary Metastases Local Therapy (7/13)

Further information:

For proven pulmonary metastases, the level of evidence for a curative approach is low, but some patients might benefit from a metastasectomy followed by an appropriate systemic treatment. In accordance with treatment of liver metastases resection of lung metastases should only be performed if R0-resection is feasible and if histological verification was done. Other procedures like thermoablation are indicated in individual cases.

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Resection

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Malignant Pleural Effusion (8/13)

Further information:

Metastatic breast cancer is the second-ranking cause of malignant pleural effusion (MPE) , resulting in dyspnoea and reduced subjective well-being.. About 10 % of all patients develop this clinical complication, in almost 50% of these cases malignant pleural effusion is the first sign of metastatic disease. Median time from primary diagnosis of the cancer to the appearance of pleural effusion is 42 months.(1) It should be treated in symptomatic cases exclusively. Tumor type, extent of involving the pleural surfaces, age and extra-pleural metastases influences the success of a pleurodesis, regardless of the sclerosing agent used. Malignant effusions due to mesothelioma and lung cancer are particularly prone to a failed procedure. (2)

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Malignant Pleural Effusion - Local Therapy (9/13)

Further information:

Thoracoscopy with Talcum pleurodesis is the treatment option of choice for malignant pleural effusion. The main procedure for chemical pleurodesis is talcum slurry. Bleomycine, Doxycycline and Mitoxantrone are individual options. Povidone-iodine can be considered as a good alternative to TTP to ensure effective pleurodesis for patients with malignant pleural effusion due to MBC. The drug is available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary.(2) There is no approval for povidone iodide in Germany.

The CALGB trial 9334 showed that bedside talcum pleurodesis was equivalent to thorascopic pleurodesis. Two randomized studies could show that indwelling pleural catheter or tunneled catheter (versus thorascopic pleurodesis) for palliation of malignant pleural effusion is a therapeutic and quality of life sustaining alternative. Retrospectively study confirmed a higher efficacy of pleurodesis followed by systemic treatment may be superior to that of systemic treatment alone with respect to local control of pleural effusions (8.5 versus 4.1 months) in breast cancer patients. Indwelling pleural catheters are indicated in individual cases. Catumaxomab is not recommended because of its side effects.

References:

VATS and talcum-pleurodesis

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Indwelling catheter/pleural drain

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2. Demmy TL, Optimal management of malignant pleural effusions (results of CALBG 30102)-. J Natl Compr Canc Netw 2012 Aug; 10 (8):975-82.
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Antibody therapy:

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Malignant Ascites - Local Therapy (10/13)

Further information:

Malignant ascites are the cancer-associated accumulation of fluids in the peritoneal cavity. The cancers most commonly associated to ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). After histological confirmation and re-evaluation of receptors the most effective treatment consist in adequate systemic treatment. Management of malignant ascites takes place in the context of palliative care and aims at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains an option in individual cases. It has to be payed attention to the side effects.

References:

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Malignant Pericardial Effusion - Local Therapy (11/13)

Further information:

Malignant pericardial effusion and cardiac tamponade remains a rarity, which are known complications of many advanced malignancies such as breast cancer, lung cancer, lymphomas and leukemias. In general overall survival is low, due to other metastatic localizations. The standard treatment of malignant effusion and cardiac tamponade has not yet been defined. Physicians should consider the status and the prognosis of each case.

In symptomatic patients drainage and fenestration are the treatment options of choice. VATS is an alternative treatment option. In individual cases US-guided puncture with instillation of mitoxantrone is possible.

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Bone Marrow Involvement Associated with Pancytopenia (12/13)

Further information:

The choice between supportive care or specific anticancer treatment for poor performance status (PS) breast cancer patients with multimetastatic disease and pancytopenia due to bone marrow involvement (BMI) often remains a clinical dilemma. If hormonal treatment options have been exhausted, concomitant weekly low-dose chemotherapy (anthracycline, paclitaxel or capecitabine) and either bisphosphonates or RANK-Ligands antibodies are indicated. Low-dose chemotherapy with epirubicin or paclitaxel as well as treatment with anti-HER2-therapy is the therapy of choice for patients with bone marrow involvement and pancytopenia. Otherwise it has been reported that even in patients with severe BMI-associated cytopenia, aggressive combination treatment regimens were effective, since most patients show improved marrow function after chemotherapy and long-lasting survival is possible.

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1. Kopp HG, et al: Symptomatic bone marrow involvement in breast cancer-clinical presentation, treatment, and prognosis: a single institution review of 22 cases. *Anticancer Res.* 2011 Nov;31(11):4025-30.
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Soft Tissue Metastasis - Local Radiotherapy (13/13)

Further information:

Local radiotherapy is the most important treatment for patients with paresis or spinal cord compression, who cannot be operated or have failed to systemic treatment. Even after surgery a concomitant radiotherapy and a systemic treatment is indicated. Plexus infiltration and other inoperable soft tissue metastasis should be treated by radiotherapy.

References:

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2. Tancioni F et al: Surgery followed by radiotherapy for the treatment of metastatic epidural spinal cord compression from breast cancer. Spine (Phila Pa 1976). 2011 Sep 15;36(20):E1352-9.
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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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CNS Metastases in Breast Cancer

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CNS Metastases in Breast Cancer – Incidence

- **Breast cancer is the 2nd most common cause of CNS metastases**
- **At autopsy:**
 - **Parenchymal CNS metastases: ~30–40%**
 - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (10 % ⇨ 40 %)**
- **Increasing incidence due to**
 - **More effective treatment of extracerebral sites with improved prognosis**
 - **Increasing use of MRI in diagnostic evaluation**
- **Lack of knowledge about treatment of brain metastases from breast cancer since most studies are not breast cancer specific. Therefore, participation in registry study Germany recommended.**

CNS Metastases in Breast Cancer (BC)

Risk Factors

- **Primary Tumor:**
 - **Negative estrogen receptor status (Basal-like cell type / triple negative)**
 - **High Grading, High Ki-67 index**
 - **HER2 and/or EGFR (HER1) overexpression**
- **Prior trastuzumab therapy in patients with metastatic BC**

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

There is no evidence for BM-screening in asymptomatic BC-patients

Graded Prognostic Assessment (GPA)

Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

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| | 0 | 0.5 | 1 | 1.5 | 2 | Score |
|-------------------|-------|------|-------|--------|------|-------|
| Prognostic Factor | | | | | | |
| KPS | 50 | 60 | 70-80 | 90-100 | n/a | _____ |
| Subtype | Basal | n/a | LumA | HER2 | LumB | _____ |
| Age, years | > 60 | < 60 | n/a | n/a | n/a | _____ |
| Sum total | | | | | | _____ |

Median survival by GPA:

GPA 0-1.0 = 3.4 months

GPA 1.5-2.0 = 7.7 months

GPA 2.5-3.0 = 15.1 months

GPA 3.5-4.0 = 25.3 months

Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive;
HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases;
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky
performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

Sperduto PW: J Clin Oncol 2012, 30:419-425.

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Independent Prognostic Factors in BM

Multivariate analyses of significant factors associated with survival after WBRT

- OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %
- Median survival time by Recursive partitioning analysis (RPA) class in months: Class I: 11.7, class II: 6.2 and class III: 3.0

| VARIABLE | P | HR | (95%-confidence interval) | |
|-------------------------------------|-------------------|-------------|---------------------------|-------------|
| SURGICAL RES | <0.0001 | 4.34 | 2.5 | 7.14 |
| SINGLE METASTASES | 0.14 | 1.08 | 0.97 | 1.21 |
| KPS >= 70 | 0.55 | 1.31 | 0.55 | 3.23 |
| BRAIN MET SCORE (BS-BM) 0.58 | | 0.63 | 0.12 | 3.29 |
| RPA | <0.0001 | 1.64 | 1.32 | 2.04 |
| CONTR PRIM TU | 0.66 | 0.92 | 0.63 | 1.34 |
| NO EXCRANIAL MET | <0.0001 | 2.38 | 1.63 | 3.44 |

Brain Metastases (1–3 lesions)

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LoE / GR

WBRT + SRS boost or neurosurgery (vs. WBRT)
Improved local control rate

2a B ++

SRS (lesions < ~ 3 cm) or neurosurgery +/- WBRT*

2b B ++

WBRT**

2b B +

Stereotactic fractionated RT (SFRT)

3b B +/-

* In individual cases additional WBRT may be omitted. Additional WBRT provides improved local control rate and symptom control but not survival benefit in all patient cohorts. Combined treatment is recommended especially in patients with single brain metastases and good performance status.

** In patients with poor prognosis and / or performance status

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy

Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

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Factors in favor of neurosurgery:

- Histological verification e.g. after a long recurrence-free interval
need for immediate decompression, life-threatening symptoms
- Tumor size > ~ 3cm not allowing stereotactic radiosurgery
- Surgically favorable location

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery

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Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation

| | after surgical resection (n=160) | | after radiosurgery (n=199) | |
|------------------|-------------------------------------|------------------|-------------------------------|------------------|
| | WBRT | observation | WBRT | observation |
| Local recurrence | 27% | 59% (p<0.001) | 19% | 31% (p=0.040) |
| New lesions | 23% | 42% (p=0.008) | 33% | 48% (p=0.023) |

- Only 12% of the patients had brain metastases from breast cancer.
- Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).
- Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.

Multiple Brain Metastases

Oxford / AGO LoE / GR

- **WBRT (add corticosteroids*)**
 - **Prolonged RT (≥ 1 week)**
- **Radiochemotherapy**
- **Chemotherapy alone**
- **Corticosteroids alone**

| | | |
|----|---|-----|
| 1a | A | ++ |
| 3b | B | ++ |
| 3b | C | +/- |
| 3a | D | +/- |
| 3a | B | +/- |

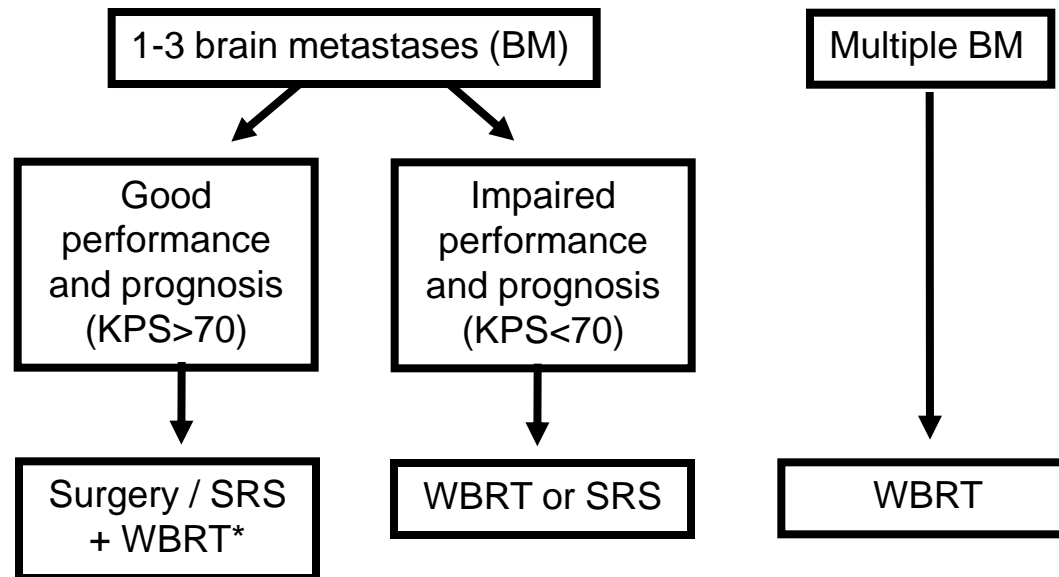
In case of radioresistance / recurrence:

- **Chemotherapy alone**
- **Lapatinib +/- Capecitabine (HER2 pos. disease)**
- **Re-radiation (if feasible)**

| | | |
|----|---|-----|
| 3a | D | +/- |
| 2b | B | + |
| 3a | D | +/- |

*Symptom adjusted therapy

Possible Treatment Approach for Brain Metastases (BM) in Breast Cancer



* In individual cases additional WBRT may be omitted. Additional WBRT after surgery/SRS provides improved local control rate and symptom control but not survival benefit in all patient cohorts.

More aggressive approach in patients with good performance status, single metastases and good prognosis recommended.

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy

Systemic and Symptomatic Therapy of Brain Metastases

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- | | | | |
|---|-----------|----------|------------|
| ➤ Continue anti-HER2-treatment in case of extracranial remission (HER2 positive) | 2c | C | + |
| ➤ Lapatinib + Capecitabine as initial treatment (HER2 positive) | 1b | B | +/- |
| ➤ Chemotherapy alone as primary treatment | 3 | D | - |
| ➤ Routine prophylactic use of anticonvulsants | 3 | C | - |
| ➤ Glucocorticoids (only when symptoms and / or mass effect) | 3 | C | ++ |

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LANDSCAPE: An FNCLCC Phase II Study with Lapatinib (L) and Capetitabine (C) in Patients with Brain Metastases (BM) from HER2-positive (+) Metastatic Breast Cancer (MBC) before Whole-brain Radiotherapy (WBRT)

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| | |
|--------------------------|---------|
| Nr. of eligible patients | N=45 |
| CNS- ORR | 67% |
| Median TTP | 5.5 Mo. |
| Median time to WBRT | 8.3 Mo. |

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Leptomeningeal Carcinomatosis

Local Therapy

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Intrathecal or ventricular therapy

| | | | |
|---|----|---|-----|
| ➤ MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue) | 2b | B | ++ |
| ➤ Liposomal cytarabine 50 mg, q 2w | 3b | C | ++ |
| ➤ Thiothepa | 3b | C | + |
| ➤ Steroids | 4 | D | +/- |
| ➤ Trastuzumab | 4 | C | +/- |

Radiotherapy

| | | | |
|---|---|---|-----|
| ➤ Focal (bulky disease) | 4 | D | + |
| ➤ WBRT | 4 | D | + |
| ➤ Neuroaxis (disseminated spinal lesions) | 4 | D | +/- |

Due to bad prognosis consider best supportive care, especially in patients with poor performance status

CNS Metastases in Breast Cancer (2/14)

No further information

No references

CNS Metastases in Breast Cancer – Incidence (3/14)

Further information:

Breast cancer represents the second most frequent etiology of brain metastasis (BM). It is estimated that 10-30 % of patients with metastatic breast cancer are diagnosed with BM. The incidence of breast cancer BM is increasing probably due to detection of subclinical disease with improved imaging techniques and increased use of imaging. Also, as systemic therapies to treat extracranial disease improve, many patients survive longer, and the frequency of CNS involvement therefore seems to be increasing.

BM are a major cause of morbidity and mortality and also impairment of quality of life. Therefore, despite major therapeutic advances in the management of patients with breast cancer, CNS metastases remain an highly relevant problem, particularly in patients with metastatic HER2-positive and triple-negative breast cancer.

Patients with CNS metastases diagnosed in Germany can be registered retrospectively and prospectively in a collaborative registry study: For further information see: <http://www.germanbreastgroup.de/>

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CNS Metastases in Breast Cancer (BC) Risk Factors (4/14)

Further information

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an “unmasking” of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

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Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/14)

Further information:

Several prognostic scores were described for risk estimation of patients with BM. One of them, the diagnosis-specific Graded Prognostic Assessment (GPA) was published to improve prognosis estimation for patients with BM. This score was validated in breast cancer patients as Breast-GPA and confirmed by analyzing a larger cohort and tumor subtypes. The Breast-GPA documents wide variation in prognosis and shows separation between subgroups of patients with breast cancer and brain metastases. This tool could aid clinical decision making and stratification in clinical trials. The published analyses describe an effect of tumor subtype on survival and show the Breast-GPA offers significantly more predictive power than the tumor subtype alone.

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Independent Prognostic Factors in BM (6/14)

Further information:

Abstract

BACKGROUND: Brain metastases (BM) are the most common form of intracranial cancer. The incidence of BM seems to have increased over the past decade. Recursive partitioning analysis (RPA) of data from three Radiation Therapy Oncology Group (RTOG) trials (1200 patients) has allowed three prognostic groups to be identified. More recently a simplified stratification system that uses the evaluation of three main prognostic factors for radiosurgery in BM was developed. **METHODS:** To analyze the overall survival rate (OS), prognostic factors affecting outcomes and to estimate the potential improvement in OS for patients with BM from breast cancer, stratified by RPA class and brain metastases score (BS-BM). From January 1996 to December 2004, 174 medical records of patients with diagnosis of BM from breast cancer, who received WBRT were analyzed. The surgery followed by WBRT was used in 15.5% of patients and 84.5% of others patients were submitted at WBRT alone; 108 patients (62.1%) received the fractionation schedule of 30 Gy in 10 fractions. Solitary BM was present in 37.9 % of patients. The prognostic factors evaluated for OS were: age, Karnofsky Performance Status (KPS), number of lesions, localization of lesions, neurosurgery, chemotherapy, absence extracranial disease, RPA class, BS-BM and radiation doses and fractionation. **RESULTS:** The OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %, respectively. The RPA class analysis showed strong relation with OS ($p < 0.0001$). The median survival time by RPA class in months was: class I 11.7, class II 6.2 and class III 3.0. The significant prognostic factors associated with better OS were: higher KPS ($p < 0.0001$), neurosurgery ($P < 0.0001$), single metastases ($p = 0.003$), BS-BM ($p < 0.0001$), control primary tumor ($p = 0.002$) and absence of extracranial metastases ($p = 0.001$). In multivariate analysis, the factors associated positively with OS were: neurosurgery ($p < 0.0001$), absence of extracranial metastases ($p < 0.0001$) and RPA class I ($p < 0.0001$). **CONCLUSION:** Our data suggests that patients with BM from breast cancer classified as RPA class I may be effectively treated with local resection followed by WBRT, mainly in those patients with single BM, higher KPS and cranial extra disease controlled. RPA class was shown to be the most reliable indicators of survival.

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Brain Metastases (1-3 lesions) (7/14)

Further information:

The optimal strategy for treatment of single brain metastases (BM) is unclear. As options, surgery or stereotactic radiotherapy are available. The therapy of BM remains controversial regarding use and timing of surgical resection, application of whole-brain radiotherapy (WBRT), stereotactic radiotherapy and systemic drugs in patients with breast cancer. Despite numerous trials, the interpretation of these has resulted in differing treatment perspectives.

In general, for patients with limited systemic disease and/or good treatment options more aggressive treatment is recommended, especially in patients with single brain metastases where most guidelines recommend combined treatment of stereotactic radiosurgery or neurosurgery and WBRT. In most cohorts, groups were divided between patients with 1-3 (sometimes 1-4) versus more metastatic sites. Radiosurgery boost with WBRT may improve local disease control in selected participants as compared to WBRT alone, although survival remains unchanged for participants with multiple brain metastases. The updated review from Tsao et al. includes a total of three randomized controlled trials examining the use of radiosurgery alone versus WBRT and radiosurgery. The addition of WBRT to radiosurgery improves local and distant brain control but there is no difference in overall survival in this analysis. Patients treated with radiosurgery alone were found to have better neurocognitive outcomes in one trial as compared to patients treated with additional WBRT and radiosurgery.

Factors in favor of primary surgery are:

Histological verification after a long recurrence-free interval, need for immediate decompression in case of rapidly developing symptoms, life-threatening symptoms, tumor size > 3.5 cm and surgically favorable location

Factors in favor of primary radiotherapy are:

RPA class II; no need for rapid decompression; short recurrence-free interval; no need for histological verification due to unambiguous medical history (e.g., additional metastatic spread); tumor location poorly amenable to surgery.

WBRT following surgery or stereotactic radiotherapy improves outcome of patients concerning symptom free survival. However, an overall survival advantage was not demonstrated for an overall patient cohorts and has to be outweighed against side effects of WBRT. For patients with good performance status and control of extra cranial disease, WBRT should be offered since some studies indicate an survival advantage.

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Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (8/14)

Further information:

See text for slide 7

Factors in favor of primary surgery are:

Histological verification after a long recurrence-free interval, need for immediate decompression in case of rapidly developing symptoms, life-threatening symptoms, tumor size > 3.5 cm and surgically favorable location

Factors in favor of primary radiotherapy are:

RPA class II; no need for rapid decompression; short recurrence-free interval; no need for histological verification due to unambiguous medical history (e.g., additional metastatic spread); tumor location poorly amenable to surgery.

No references

Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study (9/14)

Further information:

As most studies, this trial was not limited to breast cancer patients.

Abstract

PURPOSE: This European Organisation for Research and Treatment of Cancer phase III trial assesses whether adjuvant whole-brain radiotherapy (WBRT) increases the duration of functional independence after surgery or radiosurgery of brain metastases. **PATIENTS AND METHODS:** Patients with one to three brain metastases of solid tumors (small-cell lung cancer excluded) with stable systemic disease or asymptomatic primary tumors and WHO performance status (PS) of 0 to 2 were treated with complete surgery or radiosurgery and randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS). The primary end point was time to WHO PS deterioration to more than 2. **RESULTS:** Of 359 patients, 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to OBS, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO PS more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months) after OBS and 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT ($P = .71$). Overall survival was similar in the WBRT and OBS arms (median, 10.9 v 10.7 months, respectively; $P = .89$). WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, $P < .001$; radiosurgery: 31% to 19%, $P = .040$) and at new sites (surgery: 42% to 23%, $P = .008$; radiosurgery: 48% to 33%, $P = .023$). Salvage therapies were used more frequently after OBS than after WBRT. Intracranial progression caused death in 78 (44%) of 179 patients in the OBS arm and in 50 (28%) of 180 patients in the WBRT arm. **CONCLUSION:** After radiosurgery or surgery of a limited number of brain metastases, adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival.

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Multiple Brain Metastases (10/14)

Further information:

The treatment of choice for multiple BM is whole brain radiotherapy. Compared to single or limited BM, the role additional stereotactic radiotherapy is less clear.

Remission rates and duration of response were comparable between subgroups treated with regimens of 50 Gy/4 w, 40 Gy/3 w, 40 Gy/4 w, 30 Gy/2 w, 30 Gy/3 w, 20 Gy/1 w.

More hypofractionated regimens like 1×10 Gy or 2×6 Gy rapidly alleviate symptoms. However, the duration of this effect is short; therefore, these regimens are not recommended.

The addition of chemotherapy has not been proven to improve control of brain metastases in trials with breast cancer patients.

One trial examined the use of capecitabine and lapatinib instead of radiotherapy as first treatment and demonstrated some efficacy for this treatment. However, this approach was not compared to initial radiotherapy, see slide 11.

Also, some efficacy of lapatinib alone or in combination with capecitabine was observed in patients with BM progression after radiotherapy.

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Possible treatment Approach for Brain Metastases in Breast Cancer (11/14)

Further information

The management of patients with single or multiple BM depends on estimated prognosis and the aims of treatment as survival, local treated lesion control, neurocognitive preservation. As stated, the management of patients with BM from breast cancer was examined only in a few trials and most analyses are retrospective and include patients with BM of several tumor entities.

A possible treatment algorithm could be as illustrated in slide 13:

Patients with single BM and good prognosis and performance status (e.g. expected survival 3 months or more and Karnowski status > 70%): For a BM larger than 3 to 4 cm and amenable to safe surgical resection, whole brain radiotherapy (WBRT) and surgery should be considered. For single metastasis less than 3 to 4 cm, WBRT and radiosurgery or WBRT and surgery should be considered. For single brain metastasis (less than 3 to 4 cm) that are not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered. The addition of WBRT to radiosurgery or surgery offers no certain survival benefit in overall patient cohorts.

For nonresectable single brain metastasis (larger than 3 to 4 cm), WBRT should be considered (level 3).

Multiple brain metastases and good prognosis (expected survival 3 months or more): For selected patients with multiple brain metastases (all less than 3 to 4 cm), WBRT and radiosurgery, otherwise WBRT alone should be considered. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered. Patients with poor prognosis (expected survival less than 3 months): Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT.

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Systemic and Symptomatic Therapy of Brain Metastases (12/14)

Further information:

In patients without progression of extracranial metastatic disease, local therapy of BM should be performed and systemic therapy continued. Especially for anti-HER2-therapies, there is a relevant body of (retrospective) evidence for continuation of therapy despite the diagnosis of BM. This might be due to the fact that in manifest BM the permeability of the Blood Brain Barrier is decreased.

For patients with asymptomatic BM, systemic treatment should be chosen according to optimal treatment of extracranial disease.

For adults with brain metastases who have not experienced a seizure due to their metastatic brain disease, routine prophylactic use of anticonvulsants is not recommended.

For asymptomatic BM patients without mass effect no steroid treatment is recommended. Corticosteroids are recommended to provide temporary relief of symptoms related to increased intracranial pressure and edema secondary to in patients with mild symptoms related to mass effect. It is recommended for patients who are symptomatic from BM that a starting dose of 4-8 mg/day of dexamethasone is used. If patients exhibit severe symptoms with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more can be used. If corticosteroids are given, dexamethasone is the best drug choice given the available evidence. Corticosteroids should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualized treatment regimen considering the long-term sequelae of corticosteroid therapy.

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Steroids

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LANDSCAPE: An FNCLCC Phase II Study with Lapatinib (L) and Capecitabine (C) in Patients with Brain Metastases (BM) from HER2-positive (+) Metastatic Breast Cancer (MBC) before Whole-brain Radiotherapy (WBR) (13/14)

Further information:

Abstract

BACKGROUND: Brain metastases occur in 30-50% of patients with metastatic HER2-positive breast cancer. In the case of diffuse brain metastases, treatment is based on whole brain radiotherapy (WBRT). Few systemic options are available. We aimed to investigate the combination of lapatinib plus capecitabine for the treatment of previously untreated brain metastases from HER2-positive breast cancer.

METHODS: In this single-arm phase 2, open-label, multicentre study, eligible patients had HER2-positive metastatic breast cancer with brain metastases not previously treated with WBRT, capecitabine, or lapatinib. Treatment was given in 21 day cycles: patients received lapatinib (1250 mg, orally) every day and capecitabine (2000 mg/m², orally) from day 1 to day 14. The primary endpoint was the proportion of patients with an objective CNS response, defined as a 50% or greater volumetric reduction of CNS lesions in the absence of increased steroid use, progressive neurological symptoms, and progressive extra-CNS disease. All responses had to be confirmed 4 weeks after initial response. Efficacy analyses included all patients who received the study drugs and were assessable for efficacy criteria. This trial is registered with ClinicalTrials.gov, number NCT00967031.

FINDINGS: Between April 15, 2009, to Aug 2, 2010, we enrolled 45 patients, 44 (98%) of whom were assessable for efficacy, with a median follow-up of 21·2 months (range 2·2-27·6). 29 patients had an objective CNS response (65·9%, 95% CI 50·1-79·5); all were partial responses. Of all 45 treated patients, 22 (49%) had grade 3 or grade 4 treatment-related adverse events, of which the most common were diarrhoea in nine (20%) patients and hand-foot syndrome in nine (20%) patients. 14 (31%) patients had at least one severe adverse event; treatment was discontinued because of toxicity in four patients. No toxic deaths occurred.

INTERPRETATION: The combination of lapatinib and capecitabine is active as first-line treatment of brain metastases from HER2-positive breast cancer. A phase 3 trial is warranted.

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Leptomeningeal Carcinomatosis Local Therapy (14/14)

Further information:

Leptomeningeal Carcinomatosis occurs in approximately 5%-10% of all patients with metastatic breast cancer, and aggressive supportive measures are an important component of comprehensive care. Although the prognosis for those diagnosed with Leptomeningeal Carcinomatosis is poor, treatment and supportive care may allow stabilization of neurologic symptoms and afford protection from further neurologic deterioration, allowing patients to maximize their function and independence.

However, due to bad prognosis best supportive care should be considered as treatment option, especially in patients with poor performance status.

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Trastuzumab intrathecal

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MTX high dose

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Complementary Therapy

Survivorship

Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

- **Version 2002–2013:**
**Bauerfeind / Blohmer / Gerber / Göhring/
Hanf / Janni / Kümmel / von Minckwitz /
Oberhoff / Scharl / Schmidt / Schütz/
Thomssen**
- **Version 2014:**
Albert / Hanf / Fersis / Friedrich

Further
Information

References

„Alternative“ Therapies

„Integrative Oncology“

„Unconventional methods“

CAM

Complementary + alternative medicine

UCT

Unconventional Thx

Complementary

In addition to
scientifically
based medicine

Alternative

Instead of
scientifically
based medicine

Unconventional

Unproven outsider
methods

Complementary Therapy

Pre- and Postoperative

Oxford AGO
LoE / GR

Preoperative:

- Hypnosis (reduces anxiety, pain, fatigue, nausea)

1b B +/-

Postoperative:

- Acupuncture (pain relief)

2b B +/-

- Acupuncture (nausea, vomiting)

2b B +

- Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage)

1a A +

- Prophylactic lymph drainage

1b B -

Further
Information

References

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Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

**Oxford / AGO
LoE / GR**

- **Mistletoe (*Viscum album*)** in order to reduce side effects of therapy (influence on efficacy of antitumortheraPy unknown)

1a B +/-

- **Thymic peptides** (lowered the risk of severe infections)
(influence on efficacy of antitumortheraPy unknown)

2a B +/-

- **Ginseng** (in order to reduce cancer rel. fatigue)
HR-
HR+

**3b C +/-
-**

- **Ginger** (consider interaction with antitumor drugs)

1b C +/-

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Complementary Treatment Impact on Toxicity II

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| | | | |
|---|----|---|-------|
| ➤ Antioxidant supplements | 1b | B | - |
| ➤ High dose vitamine C | 1b | C | - |
| ➤ Vitamine E | 2b | D | - |
| ➤ Selenium for alleviating side effects of therapy | 1b | B | - |
| ➤ Co-Enzyme Q 10 (fatigue, QoL) | 1b | B | - |
| ➤ Proteolytic enzymes in order to reduce chemotherapy-induced toxicity | 3b | B | - |
| ➤ Chinese herbal medicine improves wound healing after mastectomy | 1b | B | -*inf |
| ➤ Oxygen and ozone therapy | 5 | D | - - |

*inf: i.v.-infusion (in Germany not approved)

Additional Complementary Therapy

Side Effects Related to Cancer Treatments

e.g. Chemotherapy

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| | Oxford LoE / GR | AGO |
|---|--------------------|------------|
| ➤ Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients | 1b B | - |
| ➤ May offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life | | |
| ➤ Homoeopathic medicines for adverse effects of cancer treatments | 1b B | +/- |
| ➤ Topical calendula ($\geq 20\%$ Calendula amount) for prophylaxis of acute dermatitis during radiotherapy | | |
| ➤ Traumeel S mouthwash to treat chemotherapy-induced stomatitis | | |
| ➤ Topical Silymarin for prophylaxis of acute dermatitis during radiotherapy | 3a B | +/- |
| ➤ Acupuncture in order to improve on | | |
| ➤ Chemotherapy-induced \geq nausea and vomiting | 1a B | + |
| ➤ Aromatase-inhibitor treatment induced arthralgia | 2b C | + |
| ➤ Cognitive dysfunction | 5 D | +/- |
| ➤ Fatigue | 1a B | +/- |
| ➤ Pain | 1a B | +/- |
| ➤ Leucopenia | 2b B | - |

Complementary Treatment

Mind-Body Medicine I

Oxford / AGO
LoE / GR

MBSR (Mindfulness-Based Stress Reduction)

Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

1b A +

Physical exercise / sport

min. 150 min. moderate endurance training per week in combination with work out exercises (2x per week) improve quality of life, cardio-respirat. fitness, physical performance and fatigue

1a A ++

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Complementary Treatment

Mind-Body Medicine II

Oxford / AGO
LoE / GR

Yoga

Improves sleep, quality of life, stress, anxiety,
depression

1b A +

Improves fatigue

2a B +/-

Qi Gong

May improve quality of life, fatigue, mood

2a B +/-

Tai Chi

Improves quality of life, physical performance

2b D +/-

Hypnosis (in combination with cognitive training)

Improves fatigue and muscle weakness under
radiation therapy

2a B +/-

Further
Information

References

Modifiable Lifestyle Factors

Prevention of Recurrence I

Oxford / AGO
LoE / GR

➤ Physical exercise

1a A ++

(Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)

➤ Smoking

1b A -

➤ Alcohol consumption (>6 g/die)

1b A -

Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis

Prevention of Recurrence II

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- **Adherence to normal BMI/weight loss if overweight**
(improves prognosis – DFS/OS)

2b B ++

- **Low fat diet**
(improves prognosis – DFS – esp. post-menopausal, ER neg.; ≤20% fat calories, only with dietary counseling!)

1b⁽⁻⁾ B +

- **Flaxseed/increased fibre intake**

2a B +/-

- **Adherence to general nutrition guidelines (e.g. DGE, WCRF)**

2a B +

- **Dietary extremes**
(are associated with less favourable outcomes)

1b B - -

Complementary Treatment

Prevention of Recurrence III

Dietary Supplements – Herbal Therapies

While on anti-cancer treatment: beware of drug interactions;

Compl./alternative methods instead of systemic treatment:

| | Oxford LoE / GR | AGO |
|--|--------------------|-----|
| ➤ Antioxidants | 2b B | -- |
| ➤ Orthomolecular substances (Selenium, Zinc...) | 5 D | - |
| ➤ Vitamines (in pts. on a balanced diet) | 2b B | - |
| ➤ Proteolytic enzymes (Papain, Trypsin, Chymotrypsin) | 3b B | - |
| ➤ Soy (phytoestrogenes) | 2b B | +/- |
| ➤ In receptor-positive tumors | | - |
| ➤ Black Cohosh (<i>Cimicifuga racemosa</i>) | 2b C | +/- |
| ➤ Mistletoe (<i>Viscum album</i>) | 1b C | - |
| ➤ Thymic peptides (impact on OS) | 2a B | - |
| ➤ Oxygen- and ozone therapy | 5 D | -- |
| ➤ Antioxidant supplements (after completion of radiotherapy) | 2b B | +/- |
| ➤ Laetrile | 1c D | -- |
| ➤ Cancer bush (<i>Sutherlandia frutescens</i>), Devil's claw (<i>Harpagophytum procumbens</i>), Rooibos tea (<i>Aspalathus linearis</i>), Bambara groundnut (<i>Vigna subterranean</i>) | 5 D | - |

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Alternatives to Reduce Menopausal Symptoms after BC I

Oxford / AGO
LoE / GR

General approaches:

- | | |
|--|--------|
| ➤ Physical exercise | 2b D + |
| ➤ Mind Body-medicine (yoga, hypnosis, education, counselling) | 1b B + |
| ➤ Acupuncture (take note: no acupuncture in tumor bearing region, possibility of cell seeding) | 1a A + |

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“Herbal” Approaches to Reduce Menopausal Symptoms

While anti-cancer treatment: Beware of drug interactions!

Oxford / AGO
LoE / GR

- | | 1b | A | - |
|--|----|---|-----|
| ➤ Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease) | | | |
| ➤ Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) | 2b | B | +/- |
| ➤ Black Cohosh for hot flushes (effectiveness could not be clearly shown) | 1b | A | +/- |
| ➤ St. John's Wort in combination-therapy (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosinkinase inhibitors) | 1b | A | -- |
| ➤ Kava-Kava (Piper methysticum) | 5 | D | -- |
| ➤ Red Clover leaf (Trifolium pratense) | 5 | D | -- |
| ➤ Dong Quai root (Angelica sinensis) | 5 | D | -- |
| ➤ Ginseng root (Panax ginseng or P. quinquefolius) | 5 | D | - |
| ➤ Bromelain + Papain + Selen + Lektin (vs. AI induced joint symptoms) | 3b | B | +/- |

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Complementary Treatment

Cancer Pain Reduction

Oxford / AGO
LoE / GR

- | | | | |
|--|----|---|-----|
| ➤ Acupuncture for cancer pain in adults | 2b | D | +/- |
| ➤ Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults | 2b | D | +/- |

Cave: No delay in diagnostic process

Further
Information

References

Immunodiagnostic Tests and Immunotherapy

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Immunodiagnostic tests:

- Analysis of:
 - Immunological parameters in peripheral blood

Oxford / AGO
LoE / GR

5 D

Local immunotherapy

- Imiquimod topically for skin metastases

4 C +/-

Systemic immunotherapy - including items below – only within clinical trials:

++

- HER2-vaccination in high risk population
- Immunomodulation (e.g. addition of Nov-2 to AC –T)
- Dendritic cell intradermal vaccination
- Active vaccination
- Passive vaccination
- Therapy with oncolytic viruses
- Cytokines

3b C +/-
5 D +/-
4 C +/-
5 D -
2b C -
4 C -
3 C -

Complementary Therapy– Survivorship (2/16)

Further information:

Screened Data Sources:

Pubmed 2003 -01/2014

ASCO 2003 – 2013

SABCS 2003 – 2012 n.d.

EBCC 2003 – 2012 n.d.

Cochrane library summary Jan. 2014:

There are 149 results out of 7646 records for: "Complementary & alternative medicine and cancer" in Record Title in Cochrane Database of Systematic Reviews"

External advice:

The commission wants to thank the following external advisors for their contribution:

2010: Advice on nutritional facts by Prof. Dr. G. Stangl, Martin-Luther-University Halle Wittenberg, Germany

2011+ 2013: Prof. Dr. G. Dobos and team,

Alfried Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen,
Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references

„Alternative“ Therapies (3/16)

Further information:

The term „alternative therapies“ has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.
- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

No references

Complementary Pre- and Postoperative Therapy (4/16)

Further information and references:

Statement on preoperative hypnosis

Briefly hypnotizing patients before they underwent breast cancer surgery reduced the amount of anesthesia administered during the operation, the level of postoperative pain, and the cost of the procedure according to an RCT with 200 patients. The patients, who were scheduled to undergo excisional breast biopsy (72%) or lumpectomy (28 %), were randomly assigned to a 15-minute presurgical hypnosis session (n = 105) conducted by a psychologist or to a nondirective empathic listener (attention control) (n = 95). Patients in the hypnosis group required less propofol (means = 64.0 versus 96.6) and lidocaine (means = 24.2 versus 31.1 mL) than patients in the control group. Patients in the hypnosis group also reported less intense postoperative pain (means = 22.4 versus 47.8 mm VAS), less unpleasantness of pain (means = 21.2 versus 39.1 mm VAS), less nausea (means = 6.6 versus 25.5 mm VAS), less fatigue (29.5 vs. 54.2 mm VAS), less discomfort (23.0 vs. 43.2 mm VAS), and less emotional upset (8.7 vs. 33.5 mm VAS). No statistically significant differences were seen in the use of fentanyl, midazolam, or recovery room analgesics.

- Montgomery GH, David D, Kangas M, Green S, Sucala M, Bovbjerg DH, Hallquist MN, Schnur JB. (2014) Randomized Controlled Trial of a Cognitive-Behavioral Therapy Plus Hypnosis Intervention to Control Fatigue in Patients Undergoing Radiotherapy for Breast Cancer. JCO DOI 10.12007JCO.2013.49.3437
- Montgomery GH, Bovbjerg DH, Schnur JB et al. (2007): A randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients. J Nat Cancer Inst; 99:1304–1312.

In another RCT ninety patients who were awaiting excisional breast biopsy were randomly assigned to undergo either a 15-minute presurgical hypnosis session (n = 49) or a 15-minute presurgical attention control session (n = 41). Results of this trial indicated that hypnosis prior to surgery helps control presurgical distress in women awaiting diagnostic breast cancer surgery.

- Schnur JB, Bovbjerg DH, David D et al. (2008): Hypnosis decreases presurgical distress in excisional breast biopsy patients. *Anesth Analg* , 106(2):440-4.

A meta-analysis across surgical settings demonstrated large effects ($d=1.2$) on emotional distress. Surgical patients in hypnosis groups had better outcomes than 89% of patients in control groups. Further beneficial effects were found on pain, pain medication, nausea, fatigue, and treatment time.

- Montgomery GH, David D, Winkel G et al. (2002): The effectiveness of adjunctive hypnosis with surgical patients: a meta-analysis. *Anesth Analg*. Jun;94(6):1639-45.

A recent review on hypnosis for cancer care conclude that the use of hypnosis for side effects of cancer surgery is strong and consistent. Clinical and cost-effectiveness has been demonstrated.

- Montgomery GH, Schnur JB, Kravits K. Hypnosis for cancer care: Over 200 years young. *CA Cancer J Clin*. 2012 Nov 20. doi: 10.3322/caac.21165.

Acupuncture and Postoperative Pain

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- Liang J, Wang LP, Wang GN et al. (2007): The effect of preemptive HAN'S acupoint nerve stimulator on postoperative pain in patients undergoing radical mastectomy. *J Harbin Med University* 41(6):607–609.
- He JP, Friedrich M, Ertan AK et al. (1999): Painrelief and movement improvement by acupuncture after ablation and axillary lymphadenectomy in patients with mammary cancer. *Clin Exp Obstet Gynecol* 26(2):81–84.

Acupuncture and Postoperative Nausea and Vomiting

- Cheong KB, Zhang JP, Huang Y, Zhang ZJ. The effectiveness of acupuncture in prevention and treatment of postoperative nausea and vomiting: A systematic review and meta-analysis. PloS One 2013 Dec;13(12): e82474
- Lee A, Fan LT.: Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD003281. Review.
- Gan TJ et al.: A Randomized Controlled Comparison of Electro-Acupoint Stimulation or Ondansetron Versus Placebo for the Prevention of Postoperative Nausea and Vomiting. Anesth Analg 2004;99:1070 –5.
- Streitberger K, Ezzo J, Schneider A et al.: Acupuncture for nausea and vomiting: an update of clinical and experimental studies. Autonomic Neuroscience: Basic and clinical 129 (2006) 107-117.

Statement on postoperative exercise

A recently published Cochrane analysis of the effects of postoperative exercise included 24 studies involving 2132 participants. The methodological quality of 10 of the 24 studies was considered adequate. Ten studies examined the effect of early versus delayed implementation of post-operative exercising. Early exercising was more effective than delayed exercising in the short term recovery of shoulder flexion ROM (abbr.: „range of movement“) (Weighted Mean Difference (WMD): 10.6 degrees; 95% Confidence Interval (CI): 4.51 to 16.6); however, early exercising also resulted in a statistically significant increase in wound drainage volume (Standardized Mean Difference (SMD) 0.31; 95% CI: 0.13 to 0.49) and duration (WMD: 1.15 days; 95% CI: 0.65 to 1.65). Fourteen studies compared the effect of structured exercising with that of the usual care. Of these, six were post-operative trials, three were carried out during adjuvant treatment, and five following cancer treatment. Structured exercise programs in the post-operative period significantly improved shoulder flexion ROM in the short run (WMD: 12.92 degrees; 95% CI: 0.69 to 25.16). Physical therapy yielded additional benefit for post-intervention shoulder function (SMD: 0.77; 95% CI: 0.33 to 1.21) and at the 6-month follow-up (SMD: 0.75; 95% CI: 0.32 to 1.19).

There was no evidence of increased risk of lymphedema from exercise at any time. The authors concluded that exercise results in a significant and clinically meaningful improvement in postoperative ROM of the shoulder in women with breast cancer. In the early post-operative period, exercising may be beneficial, although it may increase the volume and duration of wound drainage. Trials that closely monitor both exercise prescription factors (e.g., intensity) and persistent upper-limb dysfunction are needed.

- McNeely ML, Campbell K, Ospina M et al.: Exercise interventions for upper-limb dysfunction due to breast cancer treatment. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD005211. DOI: 10.1002/14651858.CD005211.pub2.

A literature review of 4 RCT's indicates that weight training exercises do not appear to increase lymphedema risk under structured conditions. All four of the studies reviewed report results of either a decrease in the development of lymphedema or no increased risk of development of lymphedema when early exercise regimens are incorporated into postoperative care.

- Cavanaugh KM.: Effects of Early Exercise on the Development of Lymphedema in Patients With Breast Cancer Treated With Axillary Lymph Node Dissection. J Oncol Pract. 2011 March; 7(2): 89–93.
- Anderson RT, Kimmick GG, McCoy TP, Hopkin J, Levine E, Miller G, Ribist P, Mihalko SL. A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial. J Cancer Surv 2012;6(2):172-81

Statement on prophylactic lymph drainage

Manual lymph drainage applied after axillary lymph node dissection for breast cancer is not effective in the short-term prevention of lymphedema of the arm.

- Devoogdt N, Christiaens MR, Geraerts I, Truijen S, Smeets A, Leunen K, Neven P, Van Kampen M.: Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial. BMJ 2011;343:d5326 doi: 10.1136/bmj.d5326

Complementary Treatment. Treatment phase. Impact on Toxicity I-II (5-6 /16)

Further information and references:

Misteltoe

The evidence from RCTs to support the view that the application of mistletoe extracts has impact on survival or leads to an improved ability to fight cancer or to withstand anticancer treatments is weak. The 5-years-data from a randomized trial with *Viscum album* additional to chemotherapy with CAF did not influence frequency of relaps or metastasis.

- Tröger W, Zdravle Z, Stankovic N, Matijasevic M: Five-year follow-up of patients with early stage breast cancer after a randomized study comparing additional treatment with *viscum album* (L.) extract to chemotherapy alone. *Breast Cancer* 2012;6:173-80

Nevertheless, there is some evidence that mistletoe extracts may offer benefits on measures of QOL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trials.

- Horneber M, Buesch, Linde K et al.: Mistletoe therapy in oncology (Review). *The Cochrane Library* 2009, Issue 2.

Thirteen prospective and controlled studies which met the inclusion/exclusion criteria reported positive effects in favor of the *Iscador* application. A random-effect meta-analysis estimated the overall treatment effect at standardized mean difference = 0.56 (CI: 0.41 to 0.71, $P < .0001$). However, the methodological quality of the studies was poor. Conclusions. The analyzed studies give some evidence that *Iscador* treatment might have beneficial short-time effects on QoL-associated dimensions and psychosomatic self-regulation.

- Büssing et al.: Quality of Life and Related Dimensions in Cancer Patients Treated with Mistletoe Extract (*Iscador*) : A Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine* Volume 2012, Article ID 219402, 8 pages.

Further references:

- Ostermann T, Raak C, Büssing A.: Survival of cancer patients treated with mistletoe extract (Iscador): a systematic literature review. BMC Cancer 2009, 9:451.
- Kienle GS, Glockmann A, Schink M et al.: Viscum album L. extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. J Exp Clin Cancer Res. 2009 Jun 11;28:79.

Thymus

In the recent Systematic Review Thymic peptides for treatment of cancer patients in addition to chemotherapy or radiotherapy, or both purified thymus extracts (pTE) and synthetic thymic peptides (sTP) were thought to enhance the immune system of cancer patients in order to fight the growth of tumour cells and to resist infections due to immunosuppression induced by the disease and antineoplastic therapy.

The authors identified 26 trials (2736 patients). Twenty trials investigated pTE (thymostimulin or thymosin fraction 5) and six trials investigated sTP (thymopentin or thymosin α 1). Twenty-one trials reported results for OS, six for DFS, 14 for TR, nine for AE and 10 for safety of pTE and sTP. Addition of pTE conferred no benefit on OS (RR 1.00, 95% CI 0.79 to 1.25); DFS (RR 0.97, 95% CI 0.82 to 1.16); or TR (RR 1.07, 95% CI 0.92 to 1.25). Heterogeneity was moderate to high for all these outcomes. For thymosin α 1 the pooled RR for OS was 1.21 (95% CI 0.94 to 1.56, $P = 0.14$), with low heterogeneity; and 3.37 (95% CI 0.66 to 17.30, $P = 0.15$) for DFS, with moderate heterogeneity. The pTE reduced the risk of severe infectious complications (RR 0.54, 95% CI 0.38 to 0.78, $P = 0.0008$; $I^2 = 0\%$). The RR for severe neutropenia in patients treated with thymostimulin was 0.55 (95% CI 0.25 to 1.23, $P = 0.15$). Tolerability of pTE and sTP was good. Most of the trials had at least a moderate risk of bias.

Overall, the authors found neither evidence that the addition of pTE to antineoplastic treatment reduced the risk of death or disease progression nor that it improved the rate of tumour responses to antineoplastic treatment. For thymosin α 1, there was a trend for a reduced risk of dying and of improved DFS. There was preliminary evidence that pTE lowered the risk of severe infectious complications in patients undergoing chemotherapy or radiotherapy.

- Wolf E, Milazzo S, Boehm K, Zwahlen M, Horneber M. Thymic peptides for treatment of cancer patients. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003993. DOI: 10.1002/14651858.CD003993.pub3.

Further References:

- Mallmann P: Einfluss einer adjuvanten kombinierten Chemo-/Immuntherapie auf immunologische Parameter und den klinischen Verlauf bei Patientinnen mit Mammakarzinom. *Zent.bl. Gynäkol.* 113 (1991) 697-706.
- Gonnelli S, Petrioli R, Cepollaro C, Palmieri R, Aquino A, Gennari C. Thymostimulin in association with chemotherapy in breast cancer patients with bone metastases. *Clinical Drug Investigation* 1995;9(2):79–87.

Ginseng

The pilot study of Barton et al. investigated whether American ginseng (*Panax quinquefolius*) helps alleviate cancer-related fatigue. In addition, they evaluated its toxicity. Eligible adults with cancer were randomized in a double-blind manner to receive American ginseng in doses of 750, 1,000, or 2,000 mg/day or placebo, divided into two daily doses for 8 weeks. Outcome measures included the Brief Fatigue Inventory, vitality subscale of the medical outcome scale Short Form-36 (SF-36), and the Global Impression of Benefit Scale at 4 and 8 weeks.

Two hundred ninety patients took part in this trial. Nonsignificant trends for all outcomes were seen in favor of the 1,000- and 2,000-mg/day doses of American ginseng. Area-under-the-curve analysis of activity interference from the Brief Fatigue Inventory was 460-467 in the placebo group and 750 mg/day group versus 480-551 in the 1,000- and 2,000-mg/day arms, respectively. Change from baseline in the vitality subscale of the SF-36 was 7.3-7.8 in the placebo and the 750-mg/day arm versus 10.5-14.6 in the 1,000- and 2,000-mg/day arms. Over twice as many patients on ginseng as on placebo perceived a benefit and were satisfied with treatment. There were no significant differences in any measured toxicities between any of the arms. Since American ginseng appears to be somewhat active and its toxicity is tolerable at 1,000-2,000 mg/day doses, further trials to evaluate its efficacy in alleviating cancer-related fatigue are warranted.

Since ginseng contains phytoestrogens, its use is discouraged for women with hormone-receptor-positive breast cancer. Depending on its dose, in vitro ginseng inhibits cytochrome P enzymes (e.g. CYP 3A4). Interactions are possible and need to be considered.

- Barton DL et al.: Pilot study of *Panax quinquefolius* (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. *Support Care Cancer*. 2010 Feb; 18(2): 179-87.
- Yong C et al.: Association of ginseng use with survival and quality of life among breast cancer patients. *Am J Epidemiol* 2006; 163(7):645-53.

- Lee Y, Jin Y, Lim W et al.: A ginsenoside-Rh1, a component of ginseng saponin, activates estrogen receptor in human breast carcinoma MCF-7 cells. J Steroid Biochem Mol Biol. 2003 Mar;84(4):463-8.
- Amato P, Christophe S, Mellon PL: Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause 2002;9:145-50.
- Sparreboom A et al.: Herbal Remedies in the United States: Potential Adverse Interactions With Anticancer Agents. J Clin Oncol 22:2489-2503.

Ginger

In this double blind, multicenter trial, 744 cancer patients were randomly assigned to four arms: 1) placebo, 2) 0.5 g ginger, 3) 1.0 g ginger, or 4) 1.5 g ginger. Nausea occurrence and severity were assessed at a baseline cycle and the two following cycles during which patients were taking their assigned study medication. All patients received a 5-HT₃ receptor antagonist antiemetic on Day 1 of all cycles. Patients took three capsules of ginger (250 mg) or placebo twice daily for 6 days starting 3 days before the first day of chemotherapy. A total of 576 patients were included in final analysis Mixed model analyses demonstrated that all doses of ginger significantly reduced acute nausea severity compared to placebo on Day 1 of chemotherapy (p=0.003). Ginger supplementation at a daily dose of 0.5 g–1.0 g significantly aids in reduction of the severity of acute chemotherapy-induced nausea in adult cancer patients.

- JL Ryan et al.: Ginger (Zingiberofficinale) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. Support Care Cancer 2012;20(7):1479-89

Preclinical studies have shown that ginger is effective as an anti-emetic agent and that it possesses 5HT₃ antagonistic activity, which is responsible for reducing chemotherapy induced nausea. The clinical data are insufficient to draw firm conclusions.

- R. Haniadka et al.: Zingiberofficinale (Ginger) as an Anti-Emetic in Cancer Chemotherapy: A Review. The Journal of Alternative and Complementary Medicine. 2012: Vol 18, No 5: 440-444.

In this pilot, randomized, open-label clinical trial, 100 women (mean age = 51.83 ± 9.18 years) with advanced breast cancer who were initially assigned to standard chemotherapy protocol with docetaxel, epirubicin, and cyclophosphamide

(the TEC regimen) were randomized to receive ginger (1.5 g/d in 3 divided doses every 8 hours) plus standard antiemetic regimen (granisetron plus dexamethasone; the ginger group) or standard antiemetic regimen alone (control group). The duration of treatment with ginger was specified to 4 days from the initiation of chemotherapy. Addition of ginger (1.5 g/d) to standard antiemetic therapy (granisetron plus dexamethasone) in patients with advanced breast cancer effectively reduces the prevalence of nausea 6 to 24 hours postchemotherapy. However, there is no other additional advantage for ginger in reducing prevalence or severity of acute or delayed CINV.

- Y. Panhai et al.: Effect of Ginger on Acute and Delayed Chemotherapy-Induced Nausea and Vomiting: A Pilot, Randomized, Open-Label Clinical Trial. Integrative Cancer Therapies, published online Feb 7, 2012.

Antioxidant supplements

Greenlee et al. (2009) concluded that current evidence on the administration of antioxidant supplements during breast cancer treatment does not suffice to provide clinicians and patients with guidelines for their use. Because of possible interactions between chemotherapy and the antioxidants selenium, coenzyme Q10, and vitamin E, these antioxidants are rated (–).

- Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.
- S.-K. Myung, Y. Kim, W. Ju et al.: Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. Annals of Oncology 21: 166–179, 2010.

Vitamin C

In their review, Ohno et al. (2009) mention case reports and clinical trials in which intravenous high-dose vitamin C prolonged survival in patients with advanced cancer. However none of the trials was randomized or placebo controlled. Two randomized clinical trials with orally administered vitamin C conducted by the Mayo Clinic did not show any benefit. Because it may interact with chemotherapy, high-dose vitamin C therapy is rated (–).

- Ohno S, Ohno Y, Suzuki N et al.: High-dose Vitamin C (Ascorbic Acid) Therapy in the Treatment of Patients with Advanced Cancer. Anticancer Res. 2009 Mar; 29(3):809-15. Review.

- Heaney M, Gardner J, Karasavvas N et al.: Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. Cancer Res. 2008 Oct 1;68(19):8031-8.

Selen

This is an updated version of the original Cochrane review published in Issue 3, 2006. Selenium supplements are frequently used by cancer patients. Selenium is an essential trace element and is involved in antioxidant protection and the redox-regulation in humans. Several adverse effects of radiotherapy and chemotherapy in cancer patients as well as cellular processes that maintain chronic lymphoedema have been linked to oxidative cell processes in the human body. Selenium has been claimed to alleviate side effects of conventional cancer therapy and recently been investigated as a remedy against chemotherapy and radiotherapy-associated side effects and secondary lymphoedema.

There is insufficient evidence at present that selenium supplementation alleviates the side effects of tumour specific chemotherapy or radiotherapy treatments or that it improves the after-effects of surgery, or improves quality-of-life in cancer patients or reduces secondary lymphoedema. To date, research findings do not provide a basis for any recommendation in favour or against selenium supplementation in cancer patients. Potential hazards of supplementing a trace mineral should be kept in mind. Since the last version of this review, the one new additional study has not provided information to change the conclusions of the original review.

- Dennert G, Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD005037. DOI: 10.1002/14651858.CD005037.pub2.

Further references:

- Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. Breast Cancer Res Treat. 2009 Jun;115(3):437-52.

Coenzym Q10

Eligible women with newly diagnosed breast cancer and planned adjuvant chemotherapy were randomized to oral supplements of 300 mg CoQ10 or placebo, each combined with 300 IU vitamin E, divided into 3 daily doses. Treatment

was continued for 24 weeks. Blood tests, QOL measures, and levels of plasma CoQ10 and vitamin E were obtained at baseline and at 8, 16, and 24 weeks.

Supplementation with conventional doses of CoQ10 led to sustained increases in plasma CoQ10 levels but did not result in improved self-reported fatigue or QOL after 24 weeks of treatment.

- Lesser GJ, Case D, Stark N, Williford S, Giguere J, Garino LA, Naughton MJ, Vitolins MZ, Lively MO, Shaw EG. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. J Support Oncol 2013;11(1):31-42

Further references:

- Lockwood K et al.: Partial and complete regression of breast cancer in patients in relation to dosage of coenzyme Q10. Biochem Biophys Res Comm 1994;199:1504-8.
- Lockwood K et al.: Progress on therapy of breast cancer with vitamin Q10 and the regression of metastasis. Biochem Biophys Res Comm 1995;212:172-7.
- Lund EL, Quistorff B, Spang-Thomsen M et al.: Effect of radiation therapy on small-cell lung cancer is reduced by ubiquinone intake. Folia Microbiol 1998;4:505-6.

Proteolytic enzymes and toxicity of chemotherapy:

Wobe Mugos(®), a mixture consisting of an extract of the calf thymus gland and enzymes (the proteases trypsin and papain) from plant and animal sources, is commonly used in complementary medicine. Data from non-randomized studies have indicated that it has multiple favorable effects, and in particular that it reduces the side effects of radiotherapy and chemotherapy in oncology patients. Patients with invasive breast cancer receiving adjuvant or palliative chemotherapy between 2005 and 2006 and who were scheduled for at least two further cycles of that specific chemotherapy were included in this pilot study of Petru et al. (2). During the preceding cycle these patients had experienced a specific toxicity of at least grade 2 according to the NCI common toxicity criteria, indicating that it was relevant to the patient. To determine whether Wobe Mugos(®) reduces the side effects in individual patients, it was coadministered during two further chemotherapy cycles, and this specific toxicity, e.g. grade 2 emesis, was again evaluated. The majority of the 57 consecutive patients received palliative chemotherapy. The enzyme therapy, orally administered as two uncracked coated tablets three times daily on all days of a chemotherapy cycle except the day of chemotherapy administration, was well

tolerated. Positive and neutral effects on toxicity parameters were observed in 11 and 42 patients, respectively, and a negative influence was observed in 4 women. Petru et al. (2) observed only a marginal influence of Wobe Mugas(®) in patients with breast cancer who had experienced at least a grade 2 toxicity in the preceding cycle and who received two further identical cycles of this chemotherapy in conjunction with the enzyme preparation. There are no randomized studies.

- Petru U, Stranz B, Petru C: Effects of proteolytic enzyme therapy with Wobe Mugas against chemotherapy-induced toxicity in breast cancer patients - results of a pilot study Wien Med Wochenschr. 2010 Nov;160(19-20):513-6.

Bromelain

- Hidaka M, Nagata M, Kawano Y, et al.: Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. Biosci Biotechnol Biochem. Feb 2008;72(2):406-411.

Chinese herbal medicine and wound healing

Skin flap ischemia and necrosis are common complications of mastectomy. Chen et al. (4) from the Sichuan University in China evaluated the influence of anisodamine and Salvia miltiorrhiza on the complications of wound healing after mastectomy for breast cancer. Ninety patients undergoing mastectomy for breast carcinoma were divided into three groups. Demographic characteristics did not differ among the groups. Group 1 received routine wound care, group 2 received intravenous Salvia miltiorrhiza after surgery for 3 days, and group 3 similarly received intravenous anisodamine. Skin flaps were observed on postoperative days 4 and 8; areas of wound ischemia and necrosis were graded and adverse events recorded. Four days after surgery the rate of ischemia and necrosis in groups 2 and 3 was significantly less than that in control group 1 (median wound score 6.80 versus 23.38, $P = 0.002$, and 3.76 versus 23.38, $P < 0.001$, respectively). This improvement in groups 2 and 3 continued to postoperative day 8 (both $P < 0.001$), but wound scores at this stage were better in group 3 than in group 2 (1.82 versus 6.92 respectively; $P = 0.022$). The volume of wound drainage was lower in group 3 than in group 1 ($P = 0.004$). The incidence of adverse effects was highest in group 3, and two patients in this group discontinued treatment. No significant complications were noted in group 2.

Anisodamine and S. miltiorrhiza were both effective in reducing skin flap ischemia and necrosis after mastectomy, although anisodamine was associated with a higher rate of adverse effects. In Germany these drugs have not been tested and are not approved for patient administration!

- Chen J, Lv Q, Yu M et al.: Randomized clinical trial of Chinese herbal medications to reduce wound complications after mastectomy for breast carcinoma. Br J Surg. 2010 Dec;97(12):1798-804.

Additional Complementary Therapy - Side effect Related to Cancer Treatments (7/16)

Further information and references:

Chinese medicinal herbs

Zhang et al. reviewed the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy-induced short term side effects in breast cancer patients.

The authors identified seven randomised controlled trials involving 542 breast cancer patients undergoing or having recently undergone chemotherapy. All studies were conducted and published in China. Authors did not pool the results because few studies were identified and no more than two used the same intervention. All were of low quality and used CMH plus chemotherapy compared with chemotherapy alone.

This review provides limited evidence about the effectiveness and safety of Chinese medicinal herbs in alleviating chemotherapy induced short term side effects. Chinese medicinal herbs, when used together with chemotherapy, may offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life, but the evidence is too limited to make any confident conclusions. Well designed clinical trials are required before any conclusions can be drawn about the effectiveness and safety of CHM in the management of breast cancer patients.

- Zhang M, Liu X, Li J, He L, Tripathy D. Chinese medicinal herbs to treat the side-effects of chemotherapy in breast cancer patients. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004921. DOI: 10.1002/14651858.CD004921.pub2
- Liao GS, Apaya MK, Shyur LF.: Herbal medicine and acupuncture for breast cancer palliative care and adjuvant therapy. Evidence-Based Complementary and Alternative Medicine 2013; 17 pages, DOI.org/10.1155/2013/437948

Homeopathic medicines for adverse effects of cancer treatments

The review evaluates the effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects of cancer treatments.

This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.

- Kassab S, Cummings M, Berkovitz S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD004845. DOI: 10.1002/14651858.CD004845.pub2.

Topical use of Silymarin

A total of 101 patients were evaluated after breast-conserving surgery followed by RT with 50.4 Gy plus boost 9–16 Gy. Of these, 51 patients were treated with the silymarin-based cream. In addition, 50 patients were documented receiving a panthenol-containing cream interventionally, if local skin lesions occurred. The median time to toxicity was prolonged significantly with silymarin-based cream (45 vs. 29 days (SOC), $p < 0.0001$). Only 9.8% of patients using silymarin-based cream showed grade 2 toxicity in week 5 of RT in comparison to 52% with SOC. At the end of RT, 23.5% of patients in the silymarin-based study group developed no skin reactions vs. 2% with SOC, while grade 3 toxicity occurred only in 2% in the silymarin-based arm compared to 28% (SOC). Silymarin-based cream Leviaderm® may be a promising and effective treatment for the prevention of acute skin lesions caused by RT of breast cancer patients. To confirm the results of this nonrandomized, observational trial, this component should be tested in larger multicenter studies in this setting.

- M. Becker-Schiebe et al.: Topical Use of a Silymarin-Based Preparation to Prevent Radiodermatitis. Strahlenther Onkol 2011;187:485–91.

Acupuncture

- Sagar SM: Acupuncture as an evidence-based option for symptom control in cancer patients. Curr Treat Options Oncol. 2008 Jun;9(2-3):117-26. Epub 2008 Aug 8. Review.

- Lu W, Dean-Clower E, Doherty-Gilman A et al.: The Value of Acupuncture in Cancer Care. *Hematol Oncol Clin N Am* (2008); 22, 631-648.

Chemotherapy-induced Nausea and Vomiting

- Ezzo J, Richardson MA, Vickers A et al.: Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting (Review). *The Cochrane Library* 2010, Issue 1.
- Fonnebo V et al.: Acupuncture and acupressure in the treatment of chemotherapy-associated nausea and vomiting. www.cam-cancer.org, Updated May 21, 2009.
- Streitberger K, Ezzo J, Schneider A: Acupuncture for nausea and vomiting: an update of clinical and experimental studies. *Autonomic Neuroscience: Basic and clinical* 129 (2006) 107-117.
- Collins K, Thomas D: Acupuncture and Acupressure for the Management of Chemotherapy-Induced Nausea and Vomiting. *JOURNAL OF THE AMERICAN ACADEMY OF NURSE PRACTITIONERS* 2004, VOLUME 16, ISSUE 2.

Cognitive dysfunction

- Johnston MF, Yang C, Hui KK et al.: Acupuncture for Chemotherapy-Associated Cognitive Dysfunction: A Hypothesis-Generating Literature Review to Inform Clinical Advice. *Integr Cancer Ther* 2007; 6; 36.

Fatigue

Three hundred two outpatients with breast cancer participated. 75 patients were randomly assigned to usual care and 227 patients to acupuncture plus usual care (random assignment of 1:3 respectively) with minimization controlling for baseline general fatigue and maintenance treatment. Treatment was delivered by acupuncturists once a week for 6 weeks through needling three pairs of acupoints (Ma 36, MP 6, Di 4). The usual care group received a booklet with information about fatigue and its management. Primary outcome was general fatigue at 6 weeks, measured with the Multidimensional Fatigue Inventory (MFI). Other measurements included the Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy–General quality-of-life scale, and expectation of acupuncture effect.

Two hundred forty-six of 302 patients randomly assigned provided complete data at 6 weeks. The difference in the mean General Fatigue score, between those who received the intervention and those who did not, was -3.11 (95% CI, -3.97 to -

2.25; $P < .001$). The intervention also improved all other fatigue aspects measured by MFI, including Physical Fatigue and Mental Fatigue (acupuncture effect, -2.36 and -1.94, respectively; both at $P < .001$), anxiety and depression (acupuncture effect, -1.83 and -2.13, respectively; both at $P < .001$), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at $P < .001$; Emotional Well-Being effect, 1.93; $P = .001$; and Social Functioning Well-Being effect, 1.05; $P < .05$).

- Molassiotis et al (2012): Acupuncture for Cancer-Related Fatigue in Patients With Breast Cancer: A pragmatic Randomized Controlled Trial. J Clin Oncol published Ahead of Print on October 29.

Further references:

- Balk J et al.: Pilot, randomized, modified, double-blind, placebo-controlled trial of acupuncture for cancer-related fatigue. J Soc Integr Oncol. 2009 Winter;7(1):4-11.
- Molassiotis A et al.: The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: a randomised controlled trial. Complement Ther Med. 2007 Dec;15(4):228-37. Epub 2006 Nov 13.
- Vickers AJ et al.: Acupuncture for postchemotherapy fatigue: a phase II study. J Clin Oncol 2004;22(9):1731-35.

Pain

- Crew KD, Capodice JL, Greenlee H et al.: Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. J Clin Oncol. 2010 Mar 1;28(7):1154-60.
- Alimi D et al.: Analgesic effect of auricular acupuncture for cancer pain: A randomized, blinded, controlled trial. J Clin Oncol 2003;21(22):4120-26.

Leucopenia

Acupuncture therapy has not been shown to prevent leucopenia. Since leucopenia may increase the risk of infection through acupuncture, patients with leucopenia should not be encouraged to undergo acupuncture treatment.

- Lu W et al.: Acupuncture for chemotherapy-induced neutropenia in patients with gynecologic malignancies: a pilot randomized, sham-controlled clinical trial. J Altern Complement Med. 2009 Jul;15(7):745-53.

ALC to prevent chemotherapy induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is common and leads to suboptimal treatment. Acetyl-L-carnitine (ALC) is a natural compound involved in neuronal protection. A total of 409 patients were evaluable (208 received ALC; 201, placebo). In a multivariate linear regression, week-12 scores were 0.9 points lower (more CIPN) with ALC than placebo (95% CI, -2.2 to 0.4; P = .17), whereas week-24 scores were 1.8 points lower with ALC (95% CI, -3.2 to -0.4; P = .01). Patients receiving ALC were more likely to have a > 5-point decrease in FACT-NTX scores (38% v 28%; P = .05), and FACT-TOI scores were 3.5 points lower with ALC (P = .03). Grade 3 to 4 neurotoxicity was more frequent in the ALC arm (eight v one). No differences between arms were observed for FACIT-Fatigue or other toxicities. Serum carnitine level increased with ALC but remained stable with placebo.

Conclusion: There was no evidence that ALC affected CIPN at 12 weeks; however, ALC significantly increased CIPN by 24 weeks. This is the first study to our knowledge showing that a nutritional supplement increased CIPN. Patients should be discouraged from using supplements without proven efficacy.

- Hershman DL, Unger JM, Crew KD, Minasian LM, Awad D, Moinpour CM, Hansen L, Lew DL, Greenlee H, Fehrenbacher L, Wade JL 3rd, Wong SF, Hortobagyi GN, Meyskens FL, Albain KS. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. J Clin Oncol. 2013 Jul 10;31(20):2627-33

Complementary Therapies - Mind-Body-Medicine I-II (8/16 and 9/16)

Further information and references:

Mind-Body Medicine (MBM)

In the absence of an adequate equivalent that does not have other connotations, the term mind/body medicine (MBM), denoting a concept of methods and therapeutic programs developed and scientifically evaluated in the United States and integrated into European medicine, has been entered everyday Speech ist Rede, language ist Sprache - NB: hat der Term das geschafftt???) in the German language. The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes for Health (NIH) defines MBM as “Practices that focus on the interactions among the brain, mind, body and behavior with the intent to use the mind to affect physical functioning and promote health.”
<http://nccam.nih.gov/health/whatiscaam/> 20.10.10

Its main goal is the activation and promotion of the patient's ability for self-regulation and thereby his or her power of self-healing in the sense of salutogenesis.

A general overview of mind/body therapies in cancer survivorship

- Monti D, Sufian M, Peterson C (2008): Potential Role of Mind-Body Therapies in Cancer Survivorship. Cancer (supplement), 112, 11:2607-2616. DOI 10.1002/CNCR.23443.

MBSR

Mindfulness based stress-reduction (MBSR) is an 8-week program, covering 24 contact-hours and 45 minutes daily home practice. The program aims at developing participants' coping resources and developing participants' mindful awareness. Thus the program consists of guided meditations, guided body scan (a specific awareness exercise) and through meditation, yoga and psychoeducation concerning stress and stress-reactions, while meditation and bodyscan is practiced at home by the use of specific audio-CDs guiding the patient.

In 2011 three systematic reviews on MBSR have been published. All of them found evidence of improved psycho-social factors which are often associated with cancer diagnosis and treatment e.g. stress, depression, reduced mood and quality of life. The review of Matchim et al. (2011) which included only women with breast cancer alone and some in heterogeneous cancer populations where breast cancer was the most common diagnosis found a large effect of MBSR on psychological symptoms, mainly stress and anxiety, but a meta-analysis was not performed.

- Matchim Y, Armer JM, Stewart BR. Mindfulness-Based Stress Reduction Among Breast Cancer Survivors: A Literature Review and Discussion. *Oncology Nurs Forum* 2011; 38 (2): 61–71.
- Musial F, Büssing A, Heusser P, Choi KE, Ostermann T. Mindfulness-based stress reduction for integrative cancer care: a summary of evidence. *Forsch Komplementmed*. 2011;18:192-202
- Shennan C, Payne S, Fenlon D. What is the evidence for the use of mindfulness-based interventions in cancer care? A review. *Psychooncology* 2011;20:681-97.

In 2012 two systematic reviews and meta-analyses in patients with breast cancer showed positive effects on the mental health of breast cancer patients. The metanalysis of Cramer et al. (2012), that included only RCT's, reported small effects on depression and moderate effects on anxiety. Zainal et al. (2012) included both RCT'S and uncontrolled trials and reported moderate to large effects on stress, depression and anxiety.

- Cramer H, Lauche R, Paul A, Dobos G. Mindfulness-based stress reduction for breast cancer - a systematic review and meta-analysis. *Curr Oncol*. 2012 Oct;19(5):e343-52.
- Zainal NZ, Booth S, Huppert FA: The efficacy of mindfulness-based stress reduction on mental health of breast cancer patients: a meta-analysis. *Psychooncology*. 2012 Sep 7. doi: 10.1002/pon.3171. [Epub ahead of print]

A recent rct of 336 women who had been operated on for breast cancer (stage I-III) found clinically meaningful, statistically significant effects of an 6 week MBSR Program in comparison to usual care on depression and anxiety after 12 months' follow-up and medium-to-large effect sizes. Another publication of the same RCT reported that MBSR had a statistically significant effect on sleep quality just after the intervention but no long-term effect.

- Würtzen H, Dalton SO, Elsass P, Sumbundu AD, Steding-Jensen M, Karlsen RV, Andersen KK, Flyger HL, Pedersen AE, Johansen C (2012). Mindfulness significantly reduces self-reported levels of anxiety and depression:

Results of a randomised controlled trial among 336 Danish women treated for stage I-III breast cancer. *Eur J Cancer.*, Dec 19. pii: S0959-8049(12)00892-1. doi: 10.1016/j.ejca.2012.10.030. [Epub ahead of print]

- Andersen SR, Würtzen H, Steding-Jessen M, Christensen J, Andersen KK, Flyger H, Mitchelmore C, Johansen C, Dalton SO: Effect of mindfulness-based stress reduction on sleep quality: Results of a randomized trial among Danish breast cancer patients. *Acta Oncol.* 2013 Jan 3. [Epub ahead of print]

A randomized controlled trial of 82 breast cancer patients found that MBSR promotes a more rapid recovery of functional T cells capable of being activated by a mitogen with the Th1 phenotype, whereas substantial recovery of B and NK cells after completion of cancer treatment appears to occur independent of stress-reducing interventions

- Lengacher CA, Kip KE, Post-White J, et al: lymphocyte Recovery After Breast Cancer Treatment and Mindfulness-Based Stress Reduction (MBSR) Therapy. *Biol Res Nurs.* 2013 Jan;15(1):37-47. doi: 10.1177/1099800411419245. Epub 2011 Nov 14.

Another RCT of MBSR (n= 68) reported improved the symptoms and quality of life of breast cancer patients across a variety of cancer symptoms and quality-of-life measures

- Lerman R, Jarski R, Rea H, Gellish R, Vicini F. Improving Symptoms and Quality of Life of Female Cancer Survivors: a Randomized Controlled Study. *Ann Surg Oncol.* 2012 Feb;19(2):373-8. doi: 10.1245/s10434-011-2051-2. Epub 2011 Sep 13.

A recent RCT of good methodological quality carried out in 229 women after surgery, chemotherapy, and radiotherapy for breast cancer, found significant improvements in mood, breast- and endocrine-related quality of life, and well-being in the MBSR group compared with standard care. These results persisted at three months.

- Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of Mindfulness-Based Stress Reduction in Mood, Breast- and Endocrine-Related Quality of Life, and Well-Being in Stage 0 to III Breast Cancer: A Randomized, Controlled Trial. *J Clin Oncol.* 2012 Apr 20;30(12):1335-42.

- Anderson SR, Würtzen H, Steding-Jessen M, Christensen J, Andersen KK, Flyger H, Mitchelmore C, Johansen C, Dalton SO. Effect of mindfulness-based stress reduction on sleep quality: results of a randomized trial among Danish breast cancer patients. *Acta Oncol* 2013 Feb;52 (2):336-44

Physical exercise

Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual's general condition, and the patient's possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 rct's of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and post-treatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.

- Schmitz KH, Courneya KS, Matthews C et al (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 42(7):1409–1426

This narrative literature review indicates that regular participation in physical activity after breast cancer diagnosis may mitigate common side effects of breast cancer adjuvant therapy, including fatigue, depression, impaired quality of life, decreased muscular strength, decreased aerobic capacity, and weight gain.

- Loprinzi PD, Cardinal BJ (2012): Effects of physical activity on common side effects of breast cancer treatment. *Breast Cancer*. 2012 Jan;19(1):4-10. doi: 10.1007/s12282-011-0292-3. Epub 2011 Jul 2. Review.

A randomized trial of exercise showed that starting a supervised exercise regimen that is tailored to an individual's strength following breast cancer surgery appears safe and may lead to improvements in physical functioning.

- Anderson RT, Kimmick GG, McCoy TP, et al: A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial. *J Cancer Surviv*. 2012 Jun;6(2):172-81. doi: 10.1007/s11764-011-0208-4. Epub 2011 Dec 10.

A systematic review identified 7 studies addressing resistance exercise (6 rct's), seven studies on aerobic and resistance exercise (3 rct's), and five studies on other exercise modalities (4 rct's). Studies concluded that slowly progressive exercise of varying modalities is not associated with the development or exacerbation of breast cancer-related lymphedema and can be safely pursued with proper supervision. Combined aerobic and resistance exercise appear safe, but confirmation requires larger and more rigorous studies. It was concluded that it is safe for breast cancer survivors to exercise throughout the trajectory of their cancer experience, including during treatment.

- Kwan ML, Cohn JC, Armer JM,: Exercise in patients with lymphedema: a systematic review of the contemporary literature. *J Cancer Surviv*. 2011 Dec;5(4):320-36.

A small study examining the effect of a home-based exercise program on lymphedema and QOL in postmastectomy patients showed that an individualized home-based exercise program led to improvement in affected upper-limb volume and circumference and QOL of postmastectomy lymphedema patients.

- Gautam AP, Maiya AG, Vidyasagar MS.: Effect of home-based exercise program on lymphedema and quality of life in female postmastectomy patients: Pre-post intervention study. *J Rehabil Res Dev*. 2011;48(10):1261-8. *J Cancer Surviv*. 2011 Dec 23. [Epub ahead of print]

A recent trial randomizing sedentary breast cancer survivors between telephone-based exercise intervention or usual care as control group reported that patients randomized to a telephone-based physical activity intervention had increased physical activity and experienced significant improvements in fitness and physical functioning.

- Ligibel JA, Meyerhardt J, Pierce JP, et al: Impact of a telephone-based physical activity intervention upon exercise behaviours and fitness in cancer survivors enrolled in a cooperative group setting. *Breast Cancer Res Treat.* 2012 Feb;132(1):205-13. doi: 10.1007/s10549-011-1882-7. Epub 2011 Nov 24.

According the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.

- Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, Bandera EV, Hamilton KK, Grant B, McCullough M, Byers T, Gansler T.: Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin.* 2012 Jul-Aug;62(4):243-74. doi: 10.3322/caac.21142. Epub 2012 Apr 26.

Exercising is contraindicated with fever or body temperature $> 38^{\circ}\text{C}$, diarrhea, vomiting, pain, acute infection (during antibiotic treatment), non-medicated hypertension, acute bleeding, bone or bone marrow metastases with a high likelihood of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin $< 8 \text{ g/dl}$, reduced consciousness, cardio- or nephrotoxicity. chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).

Further References:

- Winters-Stone KM, Dobek J, Bennett JA, The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv. 2012 Jun;6(2):189-99. doi: 10.1007/s11764-011-0210-x. Epub 2011 Dec 23.
- Baumann FT, Bloch W (2010): Evaluierte Trainingsinterventionen während und nach Tumorthherapie – eine Review-Analyse. Deut Zeit f. Sportmedizin, 61, 1: 6-10.
- De Backer, Schep G et al. (2009): Resistance Training in Cancer Survivors: a systematic review. Int Sports Med 30: 703-712.
- Ligibel JA, Campbell N, Partridge A et al. (2008): Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol 26:907–912.
- Baumann FT (2008): Bewegungstherapie und Sport bei Mamma und Prostatakarzinom – ein Überblick. Bewegungstherapie und Gesundheitssport, 24: 182-185.
- Cheema B, Gaul CA, Lane K et al. (2008): Progressive resistance training in breast cancer: a systematic review. Breast Cancer Res Treat, 109:9-26.

Statement on quality of life:

This systematic review of 9 randomized controlled trials with an average quality only presents components of exercise programmes that are effective for QoL. From this review, it is evident that aerobic exercise has a favourable effect on the QoL for patients with, and survivors of, breast cancer. Clinicians Results are optimal when performed thrice a week, at a moderate intensity (50–70% of HRmax) for greater than 30 minutes for at least 8 weeks, under supervision. This result would be regardless of the stage of breast cancer and the medical management the participants may be undergoing.

- Pastakia K, Kumar S (2011): Exercise Parameters in the Management of Breast Cancer: A Systematic Review of Randomized Controlled Trials. Physiother.Research. Res. Int. 16: 237-244.

A meta-analysis on 56 RCT's provides a comprehensive summary of studies exploring the effectiveness of a range of behavioral techniques and physical exercise interventions, during and after treatment, on long-term sequelae such as fatigue, depression, anxiety, body-image, stress and HRQoL in breast cancer patients and survivors. Statistically significant, but modest, results were found for the effect of behavioral techniques on fatigue and stress, with stronger

effects found o depression and anxiety. No significant effects were observed for body-image or HRQoL. For physical exercise interventions (17 studies), statistically significant and moderate effects were observed for fatigue, depression, body-image and HRQoL. The effect on anxiety was in the expected direction, but was not statistically significant. Only one study assessed the effect of physical exercise on stress, and thus a summary effect size could not be calculated. The results indicate that behavioral techniques and physical exercise improve psychosocial functioning and HRQoL in breast cancer patients and survivors.

- Duijts SF, Faber MM, Oldenburg HS, van Beurden M, Aaronson NK (2011): Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors-a meta-analysis. *Psycho-Oncology* 20: 115–126.

A Cochrane review of 40 (RCTs) and controlled clinical trials (CCTs) with 3694 participants indicates that exercise may have beneficial effects on HRQoL and certain HRQoL domains including cancer-specific concerns (e.g. breast cancer), body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods. Cancer diagnoses in study participants included breast, colorectal, head and neck, lymphoma, and other. Thirty trials were conducted among participants who had completed active treatment for their primary or recurrent cancer and 10 trials included participants both during and post cancer treatment. Mode of the exercise intervention included strength training, resistance training, walking, cycling, yoga, Qigong, or Tai Chi. The positive results must be interpreted cautiously due to the heterogeneity of exercise programs tested and measures used to assess HRQoL and HRQoL domains, and the risk of bias in many trials.

- Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, Snyder C. (2012): Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev.*, 15;8:CD007566. doi: 10.1002/14651858.CD007566.pub2.

The goal of this systematic review was to examine the effect of exercise on the quality of life (QOL) of women with breast cancer. Nine relevant randomized controlled trials were found, four of moderate methodological quality and five of high methodological quality. Evidence was strong that exercise positively influences QOL in women with breast cancer. Thus, exercise may be an effective means of improving QOL in women with this disease. Further research is needed to determine optimal types and parameters of appropriate exercises.

- Bicego D, Brown K (2008): Effects of Exercise on Quality of Life in Women Living with Breast Cancer: A Systematic Review. The Breast Journal,15,1: 45-51.

A review of 14 RCTs (n=717) indicated that exercise is an effective intervention to improve quality of life, cardiorespiratory fitness, and physical functioning and to decrease fatigue in breast cancer patients and survivors.

- McNeely ML, Campbell KL, Rowe BH et al. (2006): Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ, 175 (1) 34-41.

This meta-analysis of 10 studies (N = 588) indicates that aerobic exercise significantly improved cardiopulmonary function as assessed by absolute VO2 peak (standardized mean difference [SMD] 0.916, $p < 0.001$), relative VO2 peak (SMD 0.424, $p < 0.05$), and 12-minute walk test (SMD 0.502, $p < 0.001$). Similarly, aerobic exercise significantly improved body composition as assessed by percentage body fat (SMD -0.890, $p < 0.001$), but body weight and lean body mass did not change significantly. Aerobic exercise during or after cancer adjuvant therapy seems to be an effective means of improving cardiopulmonary function and decreasing the percentage of body fat in women with breast cancer.

- Kim C-J, Kang D-H, Park J-W (2009): A Meta-Analysis of Aerobic Exercise Interventions for Women with Breast Cancer. Western Journal of Nursing Research, 31,4, 437-61.
- Markes M et al. (2006): Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev. 18 Oktober, (4): CD005001.
- Shneersen C, Taskila T, Gale N, Greenfield S, Chen YF. The effect of complementary and alternative medicine on the quality of life of cancer survivors: a systematic review and meta-analyses. Complement Ther Med 2013 Aug;21(4):417-29

Statement on fatigue

This meta-analysis with twenty-eight studies (n = 2083 participants, n = 1172 with breast cancer) showed that exercise benefited individuals with cancer-related fatigue during and after cancer therapy. Further research is required to determine the optimal type, intensity, and timing of an exercise intervention.

- Cramp F, Daniel J. (2008): Exercise for the management of cancer-related fatigue in adults. Cochrane Database of Systematic Reviews, Issue 2.

This meta-analysis evaluated the effects of various exercise parameters on cancer-related fatigue (CRF) during cancer treatment. Eighteen RCTs (12 in breast cancer, 4 in prostate cancer, and 2 in other cancer patients) met all the inclusion criteria. During breast cancer treatment, home-based exercise led to a small, non-significant reduction in fatigue (standardized mean difference 0.10, 95% confidence interval -0.25 to 0.45), whereas supervised aerobic exercise showed a medium, significant reduction in CRF (standardized mean difference 0.30, 95% confidence interval 0.09 to 0.51) as compared with no exercise.

- Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM (2010): The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of Randomized Controlled Trials. Clin Oncol, 22(3):208-22.

Yoga

Mind-body interventions like yoga receive increasing attention for breast cancer survivors.

A systematic review that included 13 RCTs with a total of 760 patients found strong evidence for anxiety, stress, depression, and health-related quality of life. Effects on fatigue were inconclusive.

- Harder H, Parlour L, Jenkins V. Randomised controlled trials of yoga interventions for women with breast cancer: a systematic literature review. Support Care Cancer. 2012 Dec;20(12):3055-64. doi: 10.1007/s00520-012-1611-8.

A meta-analysis on 6 RCTs with a total of 382 patients that compared yoga to no interventions reported small effects on health-related quality of life (Hedge's $g=0.27$) but no effects on anxiety, depression, distress, sleep, and fatigue.

- Zhang J, Yang KH, Tian JH, Wang CM. Effects of yoga on psychologic function and quality of life in women with breast cancer: a meta-analysis of randomized controlled trials. J Altern Complement Med. 2012 Nov;18(11):994-1002. doi: 10.1089/acm.2011.0514. Epub 2012 Aug 21.

A more comprehensive meta-analysis on 12 RCTs and 742 patients found small to moderate effects of yoga on global health-related quality of life, functional, social, and spiritual well-being. These effects were, however, not clearly distinguishable from bias. Large effects that were present in studies with low risk of bias were found for anxiety ($g=1.51$), depression ($g=1.59$), perceived stress ($g=1.14$), and psychological distress ($g=0.86$). Subgroup analyses revealed evidence of efficacy only for yoga during active cancer treatment (chemotherapy or radiotherapy) but not in cancer survivors after completion of active treatment.

- Cramer H, Lange S, Klose P, Paul A, Dobos G. Yoga for breast cancer patients and survivors: a systematic review and meta-analysis. *BMC Cancer*. 2012 Sep 18;12:412. doi: 10.1186/1471-2407-12-412.

Finally, a meta-analysis that included 6 RCTs (including 1 RCT that was not included in the above meta-analysis of Zhang et al., 2012) with a total of 362 patients found small effects on fatigue ($g=0.33$).

- Cramer H, Lange S, Klose P, Paul A, Dobos G. Can yoga improve fatigue in breast cancer patients? A systematic review. *Acta Oncol*. 2012 Apr;51(4):559-60.
- Mustian KM, Sprod LK, Janelins M, Palesh OG, Chandwani K, Reddy PS, Melnik MK, Heckler C, Morrow GR. Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. *J Clin Oncol* 2013 Sept 10;31(28):3233-41
- Anderson SR, Würtzen H, Steding-Jessen M, Christensen J, Andersen KK, Flyger H, Mitchelmore C, Johansen C, Dalton SO. Effect of mindfulness-based stress reduction on sleep quality: results of a randomized trial among Danish breast cancer patients. *Acta Oncol* 2013 Feb;52 (2):336-44

Bhargav et al. review some mechanisms by which Yoga can positively influence cancer stem cells susceptibility to conventional cancer treatment.

Bhargav H, Metri K, Raghuram N, Ramarao NH, Koka PS. Enhancement of cancer stem cell susceptibility to conventional treatments through complementary yoga therapy: possible cellular and molecular mechanisms. *J Stem Cells*. 2012;7(4):261-7. doi: jsc.2013.7.4.261.

Qigong

The first systematic review on qigong in cancer treatment found no large RCTs. Four RCTs and 5 non-randomized trials were included. No large CRTs were found. The review found inconclusive results with some RCTs suggesting effects on overall health, and white blood cell counts. Effects on tumour progression, survival rates, and health-related quality of life were inconclusive.

- Lee, MS, Chen KW, Sancier KM et al. (2007): Qigong for cancer Treatment: A systematic review of controlled clinical trials. *Acta Oncologica*, 46: 717-722.

A more recent systematic review on qigong in supportive cancer care included 8 RCTs and 15 non-randomized trials mainly on samples with mixed types of cancer. Five of the included RCTs suggested favorable effects of qigong exercise on symptoms, inflammation, quality of life, and mood disturbance. The other 3 RCTs showed no effect. All but 1 non-randomized trials found favorable effects of qigong.

- Chan CL, Wang CW, Ho RT, Ng SM, Chan JS, Ziea ET, Wong VC. A systematic review of the effectiveness of qigong exercise in supportive cancer care. *Support Care Cancer*. 2012 Jun;20(6):1121-33. doi: 10.1007/s00520-011-1378-3.

An RCT (n=162) found improvements in QOL, fatigue, mood, and inflammation markers after qigong. The intervention was compared with TAU (treatment as usual).

Oh B, Butow P, Mullan B et al. (2010): Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized clinical trial. *Annals of Oncology* 21: 608-614.

A small study in 9 patients with histologically confirmed breast cancer awaiting surgery failed to confirm any effect on clinical changes in tumor measurements from pre- to post- qigong treatment. There was also no suggestion of change in QOL. However, this study was on external qigong, i.e. on a therapist-provided form of mental healing that is not comparable to internal qigong, i.e. patient-practiced aerobic exercise.

- Cohen L, Chen Z, Arun B, et al: External qigong therapy for women with breast cancer prior to surgery. *Integr Cancer Ther*. 2010 Dec;9(4):348-53.

Tai Chi

A 2010 systematic review on Tai Chi for breast cancer patients included 3 RCTs and 4 non-randomized controlled trials. RCTs showed no effects on quality of life, psychological, and physical outcomes. The review included a meta-analysis of 2 RCTs that failed to show effects on quality of life (Hedge's $g=0.45$; 95% Confidence Interval -0.25; 1.14). Three of the non-randomized trials found effects on quality of life, mood, self-efficacy, shoulder and upper limb function.

- Lee MS, Choi TY, Ernst E. Tai chi for breast cancer patients: a systematic review. *Breast Cancer Res Treat.* 2010 Apr;120(2):309-16. doi: 10.1007/s10549-010-0741-2.

A more recent systematic review included 4 RCTs and found limited evidence for improved physical functioning, mental health, muscle strength, quality of life, and self-esteem.

- Stan DL, Collins NM, Olsen MM, Croghan I, Pruthi S. The evolution of mindfulness-based physical interventions in breast cancer survivors. *Evid Based Complement Alternat Med.* 2012;2012:758641.

Hypnosis

In a RCT, 42 women undergoing breast cancer radiotherapy, a combination of hypnosis and cognitive therapy was compared to standard medical care. In the control group, fatigue increased linearly over the course of the radiotherapy while there was no increase in the hypnosis group. Effect size was large on the FACIT-F ($d=0.82$).

- Montgomery GH, Kangas M, David D, Hallquist MN, Green S, Bovbjerg DH, Schnur JB. Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. *Health Psychol.* 2009 May;28(3):317-22. doi: 10.1037/a0013582.

A second RCT investigated the effects of this intervention on affect and lower rates of negative affect and higher rates of positive affect in the hypnosis group than in the control group. At week 5, patients in the hypnosis group had 66% lower negative affect scores and 43% greater positive affect scores than the control group.

- Schnur JB, David D, Kangas M, Green S, Bovbjerg DH, Montgomery GH. A randomized trial of a cognitive-behavioral therapy and hypnosis intervention on positive and negative affect during breast cancer radiotherapy. J Clin Psychol. 2009 Apr;65(4):443-55. doi: 10.1002/jclp.20559.

A recent review concluded that the results of hypnosis for cancer patients undergoing are heterogeneous. The authors suggested that suggestions in the hypnosis should focus specifically on breast cancer radiotherapy and that hypnosis should be combined with cognitive therapy. (sorry das verstehe ich nicht)

- Montgomery GH, Schnur JB, Kravits K. Hypnosis for cancer care: Over 200 years young. CA Cancer J Clin. 2012 Nov 20. doi: 10.3322/caac.21165.

Modifiable Lifestyle Factors – Nutrition after Breast Cancer Diagnosis – Prevention of Recurrence I (10/16)

Further information and references:

Data on the impact of nutrition on the risk of recurrence (secondary prevention) are rare. Therefore clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007, the World Cancer Research Fund/American Institute of Cancer Research published its second expert-report.

A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project. Showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011).

However, published data of the prospective Women's Healthy Eating and Living (WHEL) study demonstrated that diet had a beneficial effect only when combined with physical activity (Pierce et al. 2007).

Nutritional advice as an adjuvant treatment can be based on recently published data from a prospective trial: the women's intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general.

Goodwin presented data indicating that adherence to a normal BMI improves disease outcome (SABCS 2009). However, being underweight seems to increase the risk of recurrence, and since up to 30% of breast cancer patients are in danger becoming cachectic, malnutrition screening seems necessary. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommends the "Malnutrition Universal Screening Tool" (MUST) for adults according to Kondrup J. et al. (Clinical Nutrition 2003;22: 415-421 www.bapen.org.uk/must_tool.html).

Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.—

Concerning cardiovascular risk factors, a recent non-randomized controlled study in breast cancer survivors comparing high fat, low carbohydrate versus low fat, high carbohydrate found a lack of evidence of a negative effect of dietary pattern on biomarkers associated with cardiovascular risk (Thompson et al, 2012)

- Thompson HJ, Sedlacek SM, Paul D, et al: Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight loss success of breast cancer survivors. *Breast Cancer Res.* 2012 Jan 6;14(1):R1. [Epub ahead of print]

Recently, more and more attention is being paid to diet quality, inflammation, and biomarkers of inflammation in breast cancer survivors (lower levels of chronic inflammation like low C-reactive protein at baseline have been associated with improved survival after breast cancer (Pierce et al, 2009)). Studies evaluating the effect of a low fat versus a low carbohydrate weight loss dietary intervention on biomarkers of long term survival in breast cancer patients like the 'CHOICE' protocol are underway, measuring inflammatory biomarkers like C-reactive protein among others (Sedlacek et al, 2011). Ongoing research.

- Pierce BL, Ballard-Barbash R, Bernstein L, et al: Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol.* 2009 Jul 20;27(21):3437-44.
- Sedlacek SM, Playdon MC, Wolfe P, et al: Effect of a low fat versus a low carbohydrate weight loss dietary intervention on biomarkers of long term survival in breast cancer patients ('CHOICE'): study protocol. *BMC Cancer.* 2011 Jul 6;11:287.

There is growing evidence that the impact of dietary factors on risk of BC differs according to the particular molecular subtypes of cancer. E.g. overweight had no prognostic impact among women with early stage triple receptor-negative BC. Supervining are the findings in the research area of nutrigenomics.

References:

Statement on adherence to normal BMI (improves prognosis – DFS/OS)

Body mass Index is an established risk factor for developing breast cancer, for its recurrence, and for early death. Obese patients have a 50 to 75% higher probability of recurrence and a 36 to 50% higher risk of dying from breast cancer. A recent observational study, however, showed that obesity plays an important role in mortality among white but not black patients with breast cancer (Lu et al, 2011).

A recent prospective investigation of pre-diagnosis body mass index (BMI) and mortality among 14,948 breast cancer patients in the After Breast Cancer Pooling Project showed that women who were underweight and morbidly obese before breast cancer diagnosis were at the greatest risk of all-cause mortality. Morbidly obese women were also at increased risk of death from breast cancer (Kwan et al, 2011). Interestingly, a recent retrospective evaluation of treatment adherence according to body weight demonstrated that patients with increasing BMI had a higher motivation and perseverance to the recommended treatment (Schmidt et al, 2011). Cave: Female patients often connote weight loss positively. Note the difference between intentional vs. unexplained (maybe as consequence of disease).

- Lu Y, Ma H, Malone KE, et al: Obesity and survival among black women and white women 35 to 64 years of age at diagnosis with invasive breast cancer. J Clin Oncol. 2011 Sep 1;29(25):3358-65.
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Goodwin presented data indicating that adherence to a normal BMI improves disease outcome (SABCS 2009). However, being underweight seems to increase the risk of recurrence, and since up to 30% of breast cancer patients are in danger

becoming cachectic, malnutrition screening seems necessary. ESPEN (The European Society for Clinical Nutrition and Metabolism) recommends the “Malnutrition Universal Screening Tool” (MUST) for adults according to Kondrup J. et al. 2003)

- Goodwin PJ, Ennis M, Pritchard KI et al. (2003): Diet and breast cancer: evidence that extremes in diet are associated with poor survival. J Clin Oncol 21:2500–2507.
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- Kellen E, Vansant G, Christiaens MR et al.: Lifestyle changes and breast cancer prognosis: a review. Breast Cancer Res Treat. 2009 Mar;114(1):13-22. doi: 10.1007/s10549-008-9990-8. Epub 2008 Apr 4. Review.

- Majed B, Moreau T, Senouci K et al.: Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Res Treat. 2008 Sep;111(2):329-42. Epub 2007 Oct 16. – weight is a prognostic factor for DFS and OS
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- Kroenke CH, Chen WY, Rosner B et al. (2005): Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23:1370–1378. – weight gain unfavourable
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Statement on low fat diet

Besides the amount of fat, fat quality (type of fat intake) seems to count, but few in vivo data so far. Lower intake of saturated fat und trans fat (in post-diagnoses diet) could be associated with improved survival after BC diagnosis.

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- Pierce JP et al.: Influence of a Diet Very High in Vegetables, Fruit, and Fiber and Low in Fat on Prognosis Following Treatment for Breast Cancer. The Women’s Healthy Eating and Living (WHEL) Randomized Trial. JAMA 2007;298(3):2891-298. – Low fat diet without influence on DFS and OS

Statement on lignans/ flaxseed

Dietary lignans make up one class of phytoestrogens and have been identified as potentially protective against breast cancer via estrogen-dependent and independent anticarcinogenic activity. Flaxseed is a major source of lignans. Lignans are metabolized by the gut microflora into enterolignans, enterolactone is the main metabolite. A recent observational study (Buck et al, 2011) found in 1,140 postmenopausal breast cancer patients that high serum enterolactone levels were associated with an improved survival. These findings were supported by a recent meta-analysis indicating a significant inverse association between serum enterolactone and postmenopausal breast cancer risk, which was stronger for ER-PR- than for ER+PR+ tumors but not differential by further expression of HER2 (Zaineddin et al, 2011). Furthermore, a recent epidemiologic study showed that higher prediagnostic plasma levels of enterolactone were related to lower mortality among breast cancer patients (Olsen et al, 2011). Accordingly, a meta-analysis showed an overall reduction of postmenopausal breast cancer risk in women with the highest vs. lowest plant lignan consumption (Buck et al 2010). However, two epidemiologic studies concerning the association of the reported dietary intake of lignans and breast cancer prognosis gave inconsistent results (McCann et al, 2009; Fink et al, 2007). These differences might be explained by the fact that a serum biomarker, which provides an index of intake, metabolism, and absorption of phytoestrogens and is not prone to recall bias and misclassification, might be a more appropriate measure. Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Besides, seeds in general are a source of dietary fiber, which itself may play a protective role as a recent meta-analysis suggests. More specifically relevant for the prevention of recurrences are data from the HEAL-study: Dietary fiber was associated with a nonsignificant inverse association with breast cancer events and total mortality.

- Belle FN, Kampman E, McTiernan A, Bernstein L, Baumgartner K, Baumgartner R, Ambis A, Ballard-Barbash R, Neuhauser ML. Dietary fiber, carbohydrates, glycemic index, and glycemic load in relation to breast cancer prognosis in the HEAL cohort. *Cancer Epidemiol Biomarkers Prev.* 2011 May;20(5):890-9. doi: 10.1158/1055-9965.EPI-10-1278. Epub 2011 Mar 23.
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The American Journal of Clinical Nutrition published „an in-depth analysis of combined evidence from cohort studies of US and Chinese women“. Overall 9514 breast cancer patients were randomized between 1991 and 2006. A significant relative risk reduction was shown: (HR: 0.75; 95% CI: 0.61, 0.92). („Slightly stronger among women with ER-negative breast cancers...“). Similar results were demonstrated by the German study (Zaineddin et al. s.o.) a significantly decreased risk for breast cancer coinciding with increased intake of soy beans, sun flower seeds and cabbage seeds independent of the patients estrogen receptor status (but statistically not significant for Lignane).

A general recommendation regarding phyto-estrogen rich or enriched food cannot be made at this time while in some studies indicate, that oral intake of soy beans decreases the effectiveness of Tamoxifen on decreasing the risk for breast cancer and while the possibility is being discussed that Daidzein (the other phyto-estrogen in soy beans next to Genistein) might enhance cell proliferation.

Moreover Nechuta et al. point out, that: „Limitation of this study should be considered. First, ..., a higher intake of isoflavones was associated with lifestyle-related factors, including regular exercise and higher consumption of cruciferous vegetables (...) and lower BMI and nonsmoking status (...). ... Further studies ... are needed.”

In conclusion: continued observation is advised. There are increasing evidence that oral intake of soy beans may translate into a health benefit for ‚survivors’. In this context other mechanisms of action of Phyto-estrogens are being discussed such as enhancing apoptosis and suppressing angiogenesis.

Nechuta SJ, Caan BJ, Chen WY, Lu W, Chen Z, Kwan ML, Flatt SW, Zheng Y, Zheng W, Pierce JP, Shu XO. Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. *Am J Clin Nutr.* 2012 Jul;96(1):123-32. doi: 10.3945/ajcn.112.035972. Epub 2012 May 30.

Statement on adherence to general nutrition guidelines

Because of rare data about the risk of recurrence (secondary prevention), clinical advice during remission is often based on the extrapolation of primary prevention data. In 2007 the World Cancer Research Fund published its second report. In summer 2012 for the first time ever the American Cancer Society published ‘Nutrition and Physical Activity Guidelines for Cancer Survivors’. Nutritional advice as an adjuvant treatment can be based on data from a prospective trial: the women’s intervention nutrition study (WINS). In this trial Chlebowsky et al. (2006) found significantly improved disease-free survival (DFS) for patients with ER-neg. tumors if less than 21% of the daily calorie intake was derived from fat. This dietary modification can only be achieved with the help of continual professional dietary counselling. The WHEL data did not confirm the beneficial effect of a low-fat diet in general. Published data of the prospective Women’s Healthy Eating and Living (WHEL) study demonstrated that diet had a (big) beneficial effect only when combined with physical activity (Pierce et al. 2007).

The primary prevention EPIC study did not show that dietary fruits and vegetables protected against breast cancer, and no data are available regarding the prevention of recurrence of BC. Nevertheless, EPIC shows an inverse association between the risk of BC overall and in postmenopausal women and adherence to Mediterranean diet, more pronounced in receptor-negative tumors (Buckland et al 2012, Masala et al 2012). And some studies suggest a lower risk of ER-tumors, which are harder to treat (e.g. Fung et al).

Finally, a recent study by Beasley et al (2011) suggests that lower intake of saturated and trans fat in the post-diagnosis diet is associated with improved survival after breast cancer diagnosis.

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Post-diagnosis dietary factors and survival after invasive breast cancer.

Beasley JM, Newcomb PA, Trentham-Dietz A, Hampton JM, Bersch AJ, Passarelli MN, Holick CN, Titus-Ernstoff L, Egan KM, Holmes MD, Willett WC.

Statement on dietary extremes (are associated with less favorable outcomes)

Dietary extremes, especially fasting excesses, are dangerous and are associated with poor survival when BMI drops pathologically low.

- Thompson HJ, Sedlacek SM, Paul D, et al: Effect of dietary patterns differing in carbohydrate and fat content on blood lipid and glucose profiles based on weight loss success of breast cancer survivors. *Breast Cancer Res.* 2012 Jan 6;14(1):R1. [Epub ahead of print]
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Modifiable Lifestyle Factors – Prevention of Recurrence II (11/16)

Further information and references:

Physical exercise

Physical training has been shown to be an efficacious adjuvant to breast cancer therapy. Physical exercise appears to be safe during and after cancer treatments and results in improvements in DFS and OS, physical functioning, quality of life, and cancer-related fatigue.

Breast cancer patients can generally be advised to avoid physical inactivity and to return to normal physical activities as soon as possible after surgery. Patients should be physically active and should exercise throughout the whole period of medical treatment. The intensity of exercise depends on the phase of medical treatment, the individual's general condition, and the patient's possibilities. Generally patients should begin exercising slowly to avoid excessive strain.

The American College of Sports Medicine (ACSM) published a comprehensive review of exercise intervention studies in breast cancer populations as part of a recent roundtable discussion of exercise in cancer survivors. The review included data from 54 RCT's of exercise in breast cancer patients: 22 in the adjuvant setting and 32 in the posttreatment setting. The authors found consistent evidence that exercise could be performed safely in both the adjuvant and posttreatment settings. Exercise led to significant improvements in aerobic fitness and strength in both settings and led to increased flexibility and physical functioning in the posttreatment setting. A moderate level of evidence also suggested that exercise led to improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition in breast cancer survivors, although findings were not always consistent. Furthermore, the ACSM guidelines cite that exercise may be associated with a reduced risk of developing a recurrence or secondary cancer.

- Schmitz KH, Courneya KS, Matthews C et al (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 42(7):1409–1426

Additionally, there is increasing evidence of an inverse relationship between exercise and markers of systemic inflammation like C-reactive protein.

- Lynch BM, Friedenreich CM, Winkler EA, et al: Associations of objectively assessed physical activity and sedentary time with biomarkers of breast cancer risk in postmenopausal women: findings from NHANES (2003-2006). *Breast Cancer Res Treat.* 2011 Nov;130(1):183-94.
- Friedenreich CM, Neilson HK, Woolcott CG, et al: Inflammatory Marker Changes in a Yearlong Randomized Exercise Intervention Trial among Postmenopausal Women. *ancer Prev Res (Phila).* 2012 Jan;5(1):98-108.

Another potential link between exercise and survival of breast cancer patients was described in a study suggesting that increasing physical activity after a breast cancer diagnosis may affect epigenetic regulation of tumor suppressor genes like L3MBTL1, which have favorable impact on survival outcomes of breast cancer patients.

- Zeng H, Irwin ML, Lu L, et al: Physical activity and breast cancer survival: an epigenetic link through reduced methylation of a tumor suppressor gene L3MBTL1. *Breast Cancer Res Treat.* 2012 May;133(1):127-35. doi: 10.1007/s10549-011-1716-7. Epub 2011 Aug 12.

According the guidelines of the American Cancer Society and the American College of Sports Medicine (Schmitz, 2010, see above) adults aged 18 to 64 years should engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Some activity is better than none and exceeding the guidelines is likely to provide additional health benefits. Activity should be done in episodes of at least 10 minutes per session and preferably spread throughout the week. Furthermore, adults should do muscle-strengthening activities involving all major muscle groups at least 2 days per week. Adults aged older than 65 years should also follow these recommendations if possible, but if chronic conditions limit activity, older adults should be as physically active as their abilities allow and avoid long periods of physical inactivity.

- Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, Bandera EV, Hamilton KK, Grant B, McCullough M, Byers T, Gansler T.: Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin.* 2012 Jul-Aug;62(4):243-74. doi: 10.3322/caac.21142. Epub 2012 Apr 26.

Exercising is contraindicated with fever or body temperature > 38°C, diarrhea, vomiting, pain, acute infection (during antibiotic treatment), non-medicated hypertension, acute bleeding, bone or bone marrow metastases with a high likelihood

of fracture, severe thrombocytopenia (under 20/ nl), circulatory problems, confusion, hemoglobin < 8 g/dl, reduced consciousness, cardio- or nephrotoxicity. chemotherapy (earliest physical activities after 1 day), or chemotherapy + Herceptin (earliest physical activities after 1 day).

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Statement on improvements in DFS and OS

Published data have shown that physical activity (PA) reduces the risk of breast cancer. However, data on the role of PA in breast cancer outcome have been inconsistent. The lack of a meta-analysis concerning this issue prompted the current report. A comprehensive search of the literature identified eight studies, two of which could be excluded. The remaining six studies (12,108 patients with breast cancer) were included in this meta-analysis. Pre-diagnosis PA reduced all causes of mortality by 18% but had no effect on breast cancer deaths. Post-diagnosis PA reduced breast cancer deaths by 34% (HR = 0.66, 95% CI, 0.57-0.77, P < 0.00001), all causes of mortality by 41% (HR = 0.59, 95% CI, 0.53-0.65, P < 0.00001), and

disease recurrence by 24% (HR = 0.76, 95% CI, 0.66-0.87, P = 0.00001). Breast cancer mortality was reduced by pre-diagnosis PA in women with body mass index (BMI) < 25 kg/m², while post-diagnosis PA reduced that risk among those with BMI ≥ 25 kg/m². On the other hand, post-diagnosis PA reduced all causes of mortality regardless of the BMI. The analysis showed that post-diagnosis PA reduced breast cancer deaths (HR = 0.50, 95% CI, 0.34-0.74, P = 0.0005) and all causes of mortality (HR = 0.36, 95% CI, 0.12-1.03, P = 0.06) among patients with estrogen-receptor (ER)-positive tumors, but not in women with ER-negative disease. The current meta-analysis provides evidence for an inverse relationship between PA and mortality in patients with breast cancer and supports the notion that breast cancer survivors should engage in appropriate PA (Ibrahim et al, 2010).

In addition, the After Breast Cancer Pooling Project (n = 13,302) reported that at least 10 MET-hours/week of PA was associated a 25% reduction in breast cancer mortality (n = 971 events, HR = 0.75, 95% CI 0.65-0.85) compared with women who did not meet the PA Guidelines (<10 MET-hours/week) (Beasley et al, 2012).

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- Pierce JP, Stefanick ML, Flatt SW et al. (2007): Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol* 25: 2345–2351.
- Borugian MJ, Sheps SB, Kim-Sing C et al. (2004): Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality from breast cancer? *Cancer Epidemiol Biomarkers Prev* 13:1163–1172.

Statement on smoking

The association of smoking with outcomes following breast cancer prognosis is not well understood.

In the LACE cohort study, 2265 women diagnosed with breast cancer were followed for a median of twelve years. Compared with never smokers, women who were current smokers had a two-fold higher rate of dying from breast cancer (HR=2.01, 95% CI 1.27–3.18] and an approximately four-fold higher rate of dying from competing (non-breast cancer) causes (HR=3.84, 95% CI 2.50–5.89).

Among seven studies that met the inclusion criteria in the systematic review, four studies reported significantly increased risk of breast cancer death with current smoking. Little evidence was found of an association between former smoking and breast cancer mortality (HR=1.24, 95% CI 0.94–1.64).

- Braithwaite D, Izano M, Moore DH et al. Smoking and survival after breast cancer diagnosis: a prospective observational study and systematic review. *Breast Cancer Res Treat.* 2012 Nov;136(2):521-33. doi: 10.1007/s10549-012-2276-1. Epub 2012 Sep 29.

Further references:

- Johnson KC, Miller AB, Collishaw NE et al.: Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tobacco Control* 2011;20:e2.
- Lee CH, Huang CS, Chen CS et al.: Overexpression and activation of the alpha9-nicotinic receptor during tumorigenesis in human breast epithelial cells. *J Natl Cancer Inst.* 2010 Sep 8;102(17):1322-35.
- Hellmann SS, Thygesen LC, Tolstrup JS et al.: Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *Eur J Cancer Prev.* 2010 Sep;19(5):366-73.

- Li CI, Daling JR, Porter PL et al.: Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. *J Clin Oncol*. 2009 Nov 10;27(32):5312-8.
- Kellen K, Vansant G, Christiaens MR et al.: Lifestyle changes and breast cancer prognosis: a review *Breast Cancer Res Treat* (2009) 114:13–22.
- Ambrosone CB, Kropp S, Yang J et al.: Cigarette smoking, N-acetyltransferase 2 genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2008 Jan;17(1):15-26.
- Holmes MD, Murin S, Chen WY et al. (2007): Smoking and survival after breast cancer diagnosis. *Int J Cancer* 120:2672–2677.
- Sagiv SK, Gaudet MM, Eng SM et al. (2007): Active and passive cigarette smoke and breast cancer survival. *Ann Epidemiol* 17:385–393.
- Hamajima N, Hirose K, Tajima K et al.: Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002 Nov 18;87(11):1234-45.
- Manjer J, Andersson I, Berglund G et al. (2000): Survival of women with breast cancer in relation to smoking. *Eur J Surg* 166:852–858.

Statement on alcohol

The association between alcohol intake and recurrence may depend on menopausal status at breast cancer diagnosis. In the international “After Breast Cancer Pooling Project” an investigation was conducted of postdiagnosis alcohol consumption among 9,329 women with a mean follow-up of 10.3 years. 58% of the women were considered drinkers (≥ 0.36 g/d, median 5.3g/d). Overall, compared with nondrinking, regular alcohol intake (≥ 6.0 g/d) was not associated with risk of recurrence. However, risk varied significantly by menopausal status. Postmenopausal women who regularly consumed alcohol (≥ 6.0 g/d) had increased risk of recurrence (HR, 1.19;95% CI, 1.01-1.40). Alcohol was not associated with mortality.

- Kwan ML, Chen WY, Flatt SW et al. Postdiagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. *Cancer Epidemiol Biomarkers Prev*. 2013 Jan;22(1):32-41. doi: 10.1158/1055-9965.EPI-12-1022. Epub 2012 Nov 13

Accordingly, alcohol intake was not associated with survival among 3146 women diagnosed with invasive breast cancer in the Swedish Mammography Cohort. Women who consumed 10 g per day (corresponding to approximately 0.75 to 1 drinks) or more of alcohol had an adjusted HR (95% CI) of breast cancer-specific death of 1.36 (0.82-2.26;p(trend)=0.47) compared with non-drinkers. Thus indicating that alcohol intake up to approximately one small drink per day does not negatively impact breast cancer-specific survival (Harris et al, 2012). This contrasts earlier findings from the LACE study showing that drinking ≥ 6 g/d of alcohol compared with no drinking was associated with an increased risk of breast cancer recurrence (HR, 1.35; 95% CI, 1.00 to 1.83) and death due to breast cancer (HR, 1.51; 95% CI, 1.00 to 2.29) (Kwan et al, 2010). Interestingly, both of these studies found an inverse relationship between alcohol intake and non- breast cancer death suggesting cardioprotective effects of alcohol on non-breast cancer death.

- Harris HR, Bergkvist L, Wolk A: Alcohol intake and mortality among women with invasive breast cancer. Br J Cancer. 2012 Jan 3.

In addition to being a risk factor for breast cancer, a high pre-diagnostic alcohol intake also seems to have an effect on the course of the disease. Holm et al. (2013) found a modest but significant association between pre-diagnostic alcohol consumption and breast cancer recurrence with a median follow-up of six years after date of diagnosis in a prospective cohort of 29,875 women. Results for breast cancer specific mortality were also suggestive of a higher risk but were not statistically significant.

Holm M, Olsen A, Christensen J, Kroman NT, Bidstrup PE, Johansen C, Overvad K, Tjønneland A. Pre-diagnostic alcohol consumption and breast cancer recurrence and mortality: results from a prospective cohort with a wide range of variation in alcohol intake. Int J Cancer. 2013 Feb 1;132(3):686-94. doi: 10.1002/ijc.27652. Epub 2012 Jun 20.

Further references:

- Kwan ML, Kushi LH, Weltzien E et al.: Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the life after cancer epidemiology study. J Clin Oncol. 2010 Oct 10;28(29):4410-6.
- Li CI, Chlebowski RT, Freiberg M et al.: Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. J Natl Cancer Inst. 2010 Sep 22;102(18):1422-31.

- Hellmann SS, Thygesen LC, Tolstrup JS et al.: Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *Eur J Cancer Prev.* 2010 Sep;19(5):366-73.
- Hong J, Holcomb VB, Tekle SA et al.: Alcohol consumption promotes mammary tumor growth and insulin sensitivity. *Cancer Lett.* 2010 Aug 28;294(2):229-35.
- Flatt SW, Thomson CA, Gold EB et al.: Low to moderate alcohol intake is not associated with increased mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2010 Mar;19(3):681-8.
- Kwan M et al (2009): Alcohol Consumption and Breast Cancer Prognosis and Survival in the Lace Study: a Prospective Cohort Study of Breast Cancer Survivors
- Kellen E, Vansant G, Christiaens MR et al.: Lifestyle changes and breast cancer prognosis: a review *Breast Cancer Res Treat* (2009) 114:13–22.
- Boyle P, Boffetta P.: Alcohol consumption and breast cancer risk. *Breast Cancer Res.* 2009;11 Suppl 3:S3.
- Reding et al.: Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young women. *Cancer Epidemiol Biomarkers Prev.* 2008; 17: 1988-1996. These results suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment.
- Zhang SM, Lee IM, Manson JE et al.: Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol.* 2007 Mar 15;165(6):667-76.
- NA HK, Mossanda KS, Lee JV et al.: Inhibition of phorbol ester-induced COX-2 expression by some edible African plants. *Biofactors* 2004;21(1-4):149-53.
- McDonald PA, Williams R, Dawkins F et al. (2002): Breast cancer survival in African American women: is alcohol consumption a prognostic indicator? *Cancer Causes Control* 13:543–549.
- Stephanie A. Smith-Warner; Donna Spiegelman et al.: Alcohol and Breast Cancer in Women A Pooled Analysis of Cohort Studies. *JAMA.* 1998;279(7):535-540 (doi:10.1001/jama.279.7.535).

Complementary Treatment - Prevention of Recurrence III (12/16)

Further information and references:

To make it quite clear: the biggest threat from unconventional therapies including CAM is from the danger of omitting evidence based therapy, in specific systemic therapy. This could be clearly demonstrated by Saquib et al (2012). The purpose of their study was to assess whether CAM use affected breast cancer prognosis in those who did not receive systemic therapy. They used a secondary data analysis of baseline/survey data from the Women's Healthy Eating and Living (WHEL) study including 2562 breast cancer survivors. Mean follow-up approached 7.3 years. Those women who did not receive any systemic treatment had a higher risk for time to additional breast cancer events (HR=1.9, 95% CI: 1.32, 2.73) and for all-cause mortality (HR=1.7, 95% CI: 1.06, 2.73) compared to those who had received systemic treatment. Among 177 women who did not receive systemic treatment, CAM use was not significantly related to additional breast cancer events. The use of dietary supplements or CAM therapies did not change this risk. This indicates that complementary and alternative therapies did not alter the outcome of breast cancer and should not be used in place of standard treatment.

- Saquib J, Parker BA, Natarajan L, Madlensky L, Saquib N, Patterson RE, Newman VA, Pierce JP. Prognosis following the use of complementary and alternative medicine in women diagnosed with breast cancer. Complement Ther Med. 2012 Oct;20(5):283-90. doi: 10.1016/j.ctim.2012.04.002. Epub 2012 Apr 27.

CAM (long-term breast cancer survivors who use CAM may have poorer emotional functioning and more medical problems than non-users)

In contrast to popular belief there's virtually no usable data on the safety and efficacy of most CAM-modalities, let alone unconventional therapies. Fortunately some CAM approaches are now being reviewed using evidence-based rationales. However, most studies are still in the protocol stage. Lin T, Ding Z, Li N, et al: Seleno-cyclodextrin sensitises human breast cancer cells to TRAIL-induced apoptosis through DR5 induction and NF-κB suppression. Eur J Cancer. 2011 Aug;47(12):1890-907.

Many other modalities listed on this slide belong to the group of unproven methods with the potential of causing side effects and drug interaction and are therefore rejected by the guideline panel (AGO -). Mistletoe and black cohosh extracts have been “uprated“ from AGO – to AGO +/- because safety data suggest that adverse outcomes are not necessarily to be feared. Soy-derived isoflavonoids are potent phytoestrogens with complete estrogenic interaction with estrogen receptors and complicated dose-response relationships in vitro. Since they could potentially stimulate ER-responsive tumor cells under unpredictable circumstances, there is a long lasting discussion whether they can be safely consumed as medical adjuvants. Guha et al showed in a cohort of 1954 breast cancer patients with diagnoses from 1997 through 2000 an inverse association between postdiagnosis soy isoflavone intake and breast cancer recurrence. However, the inverse association was not observed among women not taking tamoxifen. Contrasting these findings, a large, population-based cohort study of 5042 female breast cancer survivors in China demonstrated that soy food consumption was significantly associated with decreased risk of death and recurrence. This association was evident among women with either estrogen receptor-positive or -negative breast cancer and was present in both users and nonusers of tamoxifen (Shu et al, 2009). Occasional consumption of soy - derived foodstuff, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.

- Guha N, Kwan ML, Quesenberry CP, et al: Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat.* 2009;118(2):395–405, pmid:19221874.
- Shu XO, Zheng Y, Cai H, et al: Soy Food Intake and Breast Cancer Survival. *JAMA.* 2009 Dec 9;302(22):2437-43.
- Messina MJ, Loprinzi CL: Soy for breast cancer survivors: a critical review of the literature. *J. Nutr.* 2001 Nov;131(11 Suppl):3095S-108S.
- Zepelin HH, Meden H et al.: Isopropanolic black cohosh extract and recurrence-free survival after breast cancer. *Int. J. Clin. Pharmacol. Ther.* 2007 Mar;45(3):143-54.

Vitamins / Antioxidants

A population-based prospective cohort study of 4,877 women in Shanghai aged 20 to 75 years diagnosed with invasive breast cancer demonstrated that vitamin use shortly after breast cancer diagnosis was associated with reduced mortality and recurrence risk, adjusted for multiple lifestyle factors, sociodemographics, and known clinical prognostic factors. Women who used antioxidants (vitamin E, vitamin C, multivitamins) had 18% reduced mortality risk (HR = 0.82, 95% CI: 0.65-1.02) and 22% reduced recurrence risk (HR = 0.78, 95% CI: 0.63-0.95). The inverse association was found regardless of whether vitamin use was concurrent or nonconcurrent with chemotherapy, but was present only among patients who did

not receive radiotherapy. This does not support the current recommendation that breast cancer patients should avoid use of vitamin supplements (Nechuta et al, 2010). Greenlee and co-workers reported that frequent use of vitamin C and vitamin E in the period after breast cancer diagnosis was associated with a decreased likelihood of recurrence, whereas frequent use of combination carotenoids was associated with increased mortality. The effects of antioxidant supplement use after diagnosis likely differ by type of antioxidant.

- Nechuta S, Lu W, Chen Z, Vitamin supplement use during breast cancer treatment and survival: a prospective cohort study. *Cancer Epidemiol Biomarkers Prev.* 2011 Feb;20(2):262-71.
- Greenlee H, Kwan ML, Kushi LH, et al: Antioxidant supplement use after breast cancer diagnosis and mortality in the Life After Cancer Epidemiology (LACE) cohort. *Cancer.* 2011 Sep 27.
- Greenlee H, Hershman DL, Jacobson JS: Use of antioxidant supplements during breast cancer treatment: a comprehensive review. *Breast Cancer Res Treat.* 2009 Jun;115(3):437-52. doi: 10.1007/s10549-008-0193-0. Epub 2008 Oct 7.

Laetrile treatment for cancer

Milazzo S, Ernst E, Lejeune S, Boehm K, Horneber M. : Laetrile is the name for a semi-synthetic compound which is chemically related to amygdalin, a cyanogenic glycoside from the kernels of apricots and various other species of the genus *Prunus*. Laetrile and amygdalin are promoted under various names for the treatment of cancer although there is no evidence for its efficacy. Due to possible cyanide poisoning, laetrile can be dangerous.

The claims that laetrile or amygdalin have beneficial effects for cancer patients are not currently supported by sound clinical data. There is a considerable risk of serious adverse effects from cyanide poisoning after laetrile or amygdalin, especially after oral ingestion. The risk–benefit balance of laetrile or amygdalin as a treatment for cancer is therefore unambiguously negative.

- Milazzo S, Ernst E, Lejeune S, Boehm K, Horneber M. Laetrile treatment for cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD005476. DOI: 10.1002/14651858.CD005476.pub3.

Alternatives to reduce Menopausal Symptoms after BC I (13/16)

Further information and references:

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. Antidepressants may help with hot flashes. Acupuncture and hypnosis can also be used but the evidence is conflicting. For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl et al, 2011).

General approaches

This A wait-list controlled RCT (n=422) evaluates the effect of cognitive behavioral therapy (CBT), physical exercise (PE), and of these two interventions combined (CBT/PE) on menopausal symptoms (primary outcome), body image, sexual functioning, psychological well-being, and health-related quality of life (secondary outcomes) in patients with breast cancer experiencing treatment induced menopause. Compared with the control group, the intervention groups had a significant decrease in levels of endocrine symptoms ($P = .001$; effect size, 0.31-0.52) and urinary symptoms ($P = .002$; effect size, 0.29-0.33), and they showed an improvement in physical functioning ($P = .002$; effect size, 0.37-0.46). The groups that included CBT also showed a significant decrease in the perceived burden of hot flashes and night sweats ($P = .001$; effect size, 0.39-0.56) and an increase in sexual activity ($P = .027$; effect size, 0.65). Most of these effects were observed at both the 12-week and 6-month follow-ups.

Conclusion: CBT and PE can have salutary effects on endocrine symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. PE seems to affect primarily the frequency with which endocrine symptoms are experienced, as assessed by the FACT-ES, but not the frequency of hot flashes and night sweats specifically. CBT, in contrast, seems to not only affect symptom frequency, but also the perceived burden of hot flashes and night sweats. These results tend to support the hypothesis that cognitive and emotional factors can modify the experience of menopausal symptoms, whereas stress reduction techniques and physical exercise may have a more direct effect on menopausal symptoms via the thermoregulatory system and an improvement in overall physical condition.

- Duijts SF, van Beurden M, Oldenburg HS, Hunter MS, Kieffer JM, Stuiver MM, Gerritsma MA, Menke-Pluymers MB, Plaisier PW, Rijna H, Lopes Cardozo AM, Timmers G, van der Meij S, van der Veen H, Bijker N, de Widt-Levert LM, Geenen MM, Heuff G, van Dulken EJ, Boven E, Aaronson NK. (2012): Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol*. 2012 Nov 20;30(33):4124-33.

Physical Training

- Review: Pachman DR, Jason MJ, Loprinzi CL: Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. *International Journal of Women's Health* 2010;2 123-135.
- Lindh-Astrand L, Nedstrand E, Wyon Y et al.: Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. *Maturitas*. 2004 Jun 15;48(2):97-105.

Mind-Body-Medicine (Relaxation training, Yoga, Hypnosis)

- Review: Pachman DR, Jason MJ, Loprinzi CL: Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. *International Journal of Women's Health* 2010;2 123-135.
- Tremblay A, Sheeran L, Aranda SK: Psychoeducational interventions to alleviate hot flashes: a systematic review. *Menopause: The Journal of The North American Menopause Society* Vol. 15, No. 1, pp. 193/202.

A unique relaxation training consisting of deep breathing, imagination, and PME and subsequent independent practicing at home with an audiotape for 20 minutes daily one month long significantly decreased the frequency and intensity of hot flashes in n=76 women compared with n=74 women with no intervention.

- Fenlon DR, Corner JL, Haviland JS (2008): A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer. *J Pain Symptom Manage*. Apr;35(4):397-405.

Yoga (n=17), 8 monthly 120-minute units, compared with waitinglist (n=20). Result: Significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. These results remain significant after 3 months follow-up.

- Carson JW, Carson KM, Porter LS et al. (2009): Yoga of. Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. Support Care Cancer, 17: 1301-1309.

RCT (n=51): 5 weekly hypnosis sessions (ca. 50 min.) and instructions on self-hypnosis compared with waiting list. Results: hot flash scores (frequency x average severity) decreased 68% compared with control group. In addition significant improvement in anxiety, depression, and sleep.

- Elkins G, Marcus J et al. (2008): Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. Journal of Clinical Oncology 26(31): 5022-6.

Vaginal Lubricants

- Trinkaus M, Chin S, Wolfman W et al.: Should urogenital atrophy in breast cancer survivors be treated with topical estrogens? Oncologist. 2008 Mar;13(3):222-31.
- Loibl S, Lintermans A, Dieudonné AS, Neven P. Management of menopausal symptoms in breast cancer patients. Maturitas. 2011 Feb;68(2):148-54.

Acupuncture

In their review Lee et al. assessed the effectiveness of acupuncture as a treatment option for hot flashes in patients with breast cancer. They searched the literature using 14 databases from their inceptions to August 2008, without language restrictions. They included randomized clinical trials (RCTs) comparing real with sham acupuncture or another active treatment or no treatment. Methodological quality of the trials was assessed using the modified Jadad score. Three RCTs compared the effects of manual acupuncture with sham acupuncture. One RCT showed that acupuncture reduced hot flash frequency, while the other two RCTs did not. The meta-analysis showed significant effects of acupuncture compared with sham acupuncture (n = 189, weight mean difference, 3.09, 95% confidence intervals -0.04 to 6.23, P = 0.05) but marked heterogeneity was observed in this model (chi (2) = 8.32, P = 0.02, I (2) = 76%). One RCT compared the effects of

electroacupuncture (EA) with hormone replacement therapy. Hormone therapy was more effective than EA. Another RCT compared acupuncture with venlafaxine and reported no significant intergroup difference. A further RCT compared acupuncture with applied relaxation and failed to show a significant intergroup difference. Lee et al. concluded that acupuncture is not an effective treatment for hot flashes in patients with breast cancer. Further research is required to determine whether acupuncture is suitable for treating hot flashes in patients with breast cancer.

- Lee MS, Kim KH, Choi SM et al.: Acupuncture for treating hot flashes in breast cancer patients: a systematic review. *Breast Cancer Res Treat* (2009) 115:497–503.

In contrast to this, in a recent trial 94 women were randomized into three study arms: 31 had acupuncture, 29 had sham acupuncture and 34 had no treatment. In the acupuncture group, 16 patients (52%) experienced a significant effect on hot flashes compared with seven patients (24%) in the sham group ($p < 0.05$). The effect came after the second acupuncture session and lasted for at least 12 weeks after last treatment. A statistically significant positive effect was seen on sleep in the acupuncture group compared with the sham-acupuncture and no-treatment groups. The effect was not correlated with increased levels of plasma estradiol. No side effects of acupuncture were registered.

In this study acupuncture significantly relieves hot flashes and sleep disturbances and is a good and safe treatment in women treated for breast cancer. The project is registered at Clinical Trials.gov (no: NCT00425776).

- S. Bokmand et al (2012): Acupuncture relieves menopausal discomfort in breast cancer patients: A prospective, double blinded, randomized study. *Breast* 2012 Aug 17. [Epub ahead of print]

In another trial with breast cancer survivors, acupuncture was compared with venlafaxine. It was demonstrated that acupuncture appears to be equivalent to drug therapy in these patients. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with breast cancer (Walker et al, 2010).

- Walker EM, Rodriguez AI, Kohn B et al.: Acupuncture Versus Venlafaxine for the Management of Vasomotor Symptoms in Patients With Hormone Receptor-Positive Breast Cancer: A Randomized Controlled Trial. *J Clin Oncol*. 2010 Feb 1;28(4):634-40.

However, in the trial of Deng et al. acupuncture and sham-acupuncture both reduced hot flash symptoms. After the cross-over, the initial sham-acupuncture group further improved after receiving true acupuncture treatment.

- Deng G et al.: Randomized, Controlled Trial of Acupuncture for the Treatment of Hot Flashes in Breast Cancer Patients. J Clin Oncol 2007; 25:5584-5590.

In the trial of Nedstrand et al. acupuncture and relaxation therapy were equally successful in reducing hot flashes. Acupuncture was also as effective as venlafaxin in reducing the symptoms.

- Nedstrand E et al.: Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electro-acupuncture: a preliminary study. Climateric 2005; 8:243-250.

Finally, a word of caution: acupuncture should be used by knowledgeable practitioners applying general medically sensed caution. A case report by Tseng et al (2011) sheds light of the potential risks: acupuncture in TCM with needles placed into a cutaneous tumor manifestation resulted in disseminated skin metastases. Notwithstanding the beneficial effects referenced above, even measures like acupuncture have their specific risks and should not be applied uncritically.

- Tseng HS, Chan SE, Kuo SJ, Chen DR. Acupuncture-related rapid dermal spread of breast cancer: a rare case. J Breast Cancer. 2011 Dec;14(4):340-4. doi: 10.4048/jbc.2011.14.4.340. Epub 2011 Dec 27.

Further references:

- Lu W, Rosenthal DS: Recent Advances in Oncology: Acupuncture and Safety, Considerations in Practice. Current Treatment Options in Oncology (2010) 11:141–146.
- Crew K et al.: Randomized, Blinded, Sham-Controlled Trial of Acupuncture for the Management of Aromatase Inhibitor–Associated Joint Symptoms in Women With Early-Stage Breast Cancer. J Clin Oncol. 2010; 28:1154-1160.
- Hervik J, Mjåland O: Acupuncture for the treatment of hot flashes in breast cancer patients, a randomized, controlled trial. Breast Cancer Res Treat. 2009 Jul;116(2):311-6.
- Vincent A, Barton DL, Mandrekar JN et al.: Acupuncture for hot flashes: a randomized, sham-controlled clinical study. Menopause. 2006 Oct 2.

- Davies FM (2001): The effect of acupuncture treatment on the incidence and severity of hot flushes experienced by women following treatment for breast cancer: a comparison of traditional and minimal acupuncture. *Eur J Cancer* 37:S438–S438. doi: 10.1016/S0959-8049(01)82079-7.
- Soo Lee M, Kim KH, Choi SM et al.: Acupuncture for treating hot flashes in breast cancer patients: a systematic review *Breast Cancer Res Treat* DOI 10.1007/s10549-008-0230-z.

Herbal Approaches to Reduce Menopausal Symptoms - (14/16)

Further information and references:

Roberts reviewed and summarised current evidence on the efficacy and safety of herbal medicinal products for the relief of hot flushes in women with previous breast cancer. The majority of studies, regarding the efficacy of herbal treatments for hot flushes, have not been conducted in women with breast cancer and many are of short duration. Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions.

- Roberts H. Safety of herbal medicinal products in women with breast cancer. *Maturitas*. 2010 Aug;66(4):363-9. doi: 10.1016/j.maturitas.2010.02.010. Epub 2010 Mar 27.

More recently, Ma et al (2011) review a diverse array of estrogenic botanical supplement (EBS) to find out whether the use influences breast cancer survivors' health-related outcomes. The findings were also very diverse and indicated that several specific types of EBS might have important influences on a woman's various aspects of quality of life, but further verification is necessary. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating (all OR approximately 0.4 and all 95% CIs exclude 1). This is the reason, why we change the AGO recommendation from -- to -.

Ma H, Sullivan-Halley J, Smith AW, Neuhaus ML, Alfano CM, Meeske K, George SM, McTiernan A, McKean-Cowdin R, Baumgartner KB, Ballard-Barbash R, Bernstein L. Estrogenic botanical supplements, health-related quality of life, fatigue, and hormone-related symptoms in breast cancer survivors: a HEAL study report. *BMC Complement Altern Med*. 2011 Nov 8;11:109. doi: 10.1186/1472-6882-11-109.

- Pachman DR, Jason MJ, Loprinzi CL: Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. *International Journal of Women's Health* 2010;2 123-135.

- NIH State-of-the-Science Panel on Management of Menopause-Related Symptoms. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med*. 2005;142(12 Pt 1):1003–1013.
- Carroll DG, Kelley KW: Use of antidepressants for management of hot flashes. *Pharmacotherapy*. 2009 Nov;29(11):1357-74.
- Bardia A, Novotny P, Sloan J et al.: Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis. *Menopause*. 2009 May-Jun;16(3):477-83.

Phytoestrogens

Soy-derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated. Since they have the potential to stimulate ER-responsive tumor cells under unpredictable circumstances, they should not be consumed as medical adjuvants. For the same reason the use of red clover, ginseng and dong quai as medical adjuvants should be discouraged. However, the occasional consumption of soy - derived foodstuffs, e.g., tofu or soy milk, as part of a vegetable-based diet is probably harmless.

- Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. *Crit Rev Toxicol*. 2011 41(6):463-506.
- Lethaby AE, Brown J, Marjoribanks J et al.: Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2007(4):CD001395.
- Nelson HD, Vesco KK, Haney E et al.: Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *Jama*. 2006;295(17):2057–2071.
- Howes LG, Howes JB, Knight DC: Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. *Maturitas*. 2006; 55(3):203–211.
- Liu B, Edgerton S, Yang X, Kim A et al.: Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. *Cancer Res* 2005;65:879–86.
- Chen J, Hui E, Ip T et al.: Dietary flaxseed enhances the inhibitory effect of tamoxifen on the growth of estrogen-dependent human breast cancer (mcf-7) in nude mice. *Clin Cancer Res*. 2004; 10(22):7703–7711.

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Flaxseed

Concerning the occurrence of hot flushes, a recent randomized phase III trial failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi et al, 2012). Flower et al very recently performed a systematic review of the current literature and concluded that current evidence suggests that flax may be associated with decreased risk of breast cancer. Flax demonstrates antiproliferative effects in breast tissue of women at risk of breast cancer and may protect against primary breast cancer. Mortality risk may also be reduced among those living with breast cancer.

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Black cohosh (Cimicifuga racemosa)

= (Phyto-SERM = selective estrogen receptor modulator)

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St John's Wort

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Red clover

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Dong Quai

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Ginseng root

In a case-control study conducted in Korea, ginseng intakers had a decreased risk [odds ratio = 0.50, 95% confidence interval (CI) = 0.44-0.58] for cancer compared with nonintakers. However, breast cancer, there was no association with ginseng intake.

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Bromelain+Papain+Selen+Lektin bei AI-induzierten Gelenkbeschwerden

- Uhlenbruck B, Van Leendert R, Schneider B et al.: Reduced side-effects of adjuvant hormone therapy in breast cancer patients by complementary medicine. *In Vivo.* 2010 Sep-Oct;24(5):799-802.

A clinical investigation (representing evidence-based medicine level III) of Uhlenbruck et al. (3) was performed to evaluate the benefit of complementary medicine in breast cancer patients undergoing adjuvant hormone therapy (HT). The patients (n=129) were treated according to international guidelines. All patients suffered from arthralgia and mucosal dryness induced by the adjuvant HT. To reduce these side effects, the patients were administered a combination of sodium selenite, proteolytic plant enzymes (bromelain and papain), and *Lens culinaris* lectin as a complementary treatment. On the basis of case report formulas (CRFs), the patients' self assessments of defined side-effects of HT (arthralgia and mucosal dryness) were documented before as well as 4 and 8 weeks after complementary treatment. Results were validated by scoring from 1 (no side-effects/optimal tolerability) to 6 (extreme side-effects/extremely bad tolerability). The severity of side effects of HT was reduced by the complementary treatment with sodium selenite, plant enzymes (bromelain and papain) and *Lens culinaris* lectin. The mean score of symptoms declined from 4.2 (before treatment) to 3.2 (after 4 weeks of treatment) to 2.7 (after 8 weeks of treatment) for arthralgia and from 3.2 (before treatment) to 2.9 (after 4 weeks of treatment) to 2.6 (after 8 weeks of treatment) for mucosal dryness, the primary aims of this investigation. The reduction of

side effects of HT was statistically significant ($p < 0.001$ after 4 weeks and $p < 0.0001$ after 8 weeks). This investigation demonstrated the benefits of indication-based complementary treatment in breast cancer patients, e.g., reduction of the side effects of adjuvant HT. A randomized controlled trial is planned to integrate the complementary treatment of sodium selenite combined with proteolytic enzymes._

Complementary Treatment: Cancer Pain reduction (15/16)

Further information and references:

A total of 15 RCTs met the inclusion criteria of this systematic review. All of the included RCTs were associated with a high risk of bias. The majority of acupuncture treatments or combination therapies with analgesics exhibited favourable effects compared with conventional treatments in individual studies. However, a meta-analysis suggested that acupuncture did not generate a better effect than drug therapy (n0886; risk ratio (RR), 1.12; 95% CI 0.98 to 1.28; P00.09). The comparison between acupuncture plus drug therapy and drug therapy alone demonstrated a significant difference in favour of the combination therapy (n0437; RR, 1.36; 95% CI 1.13 to 1.64; P00.003). The results of this systematic review provide no strong evidence for the effectiveness of acupuncture in the management of cancer pain.

- TY Choi et al (2012): Acupuncture for the treatment of cancer pain: a systematic review of randomized clinical trials. Support Care Cancer 20:1147-1158.

Forty percent of individuals with early or intermediate stage cancer and 90% with advanced cancer have moderate to severe pain and up to 70% of patients with cancer pain do not receive adequate pain relief. It has been claimed that acupuncture has a role in management of cancer pain and guidelines exist for treatment of cancer pain with acupuncture. Three RCTs (204 participants) were included in this review.

There is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults.

- Paley CA, Johnson MI, Tashani OA, Bagnall AM. Acupuncture for cancer pain in adults. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007753. DOI: 10.1002/14651858.CD007753.pub2.

More recently a similar result was extracted from a systematic literature review by Garcia et al (2013). The authors concluded that acupuncture is an appropriate adjunctive treatment for chemotherapy-induced nausea/vomiting. For other symptoms (including pain), efficacy remains undetermined.

- Garcia MK, McQuade J, Haddad R, Patel S, Lee R, Yang P, Palmer JL, Cohen L. Systematic review of acupuncture in cancer care: a synthesis of the evidence. J Clin Oncol. 2013 Mar 1;31(7):952-60. doi: 10.1200/JCO.2012.43.5818. Epub 2013 Jan 22.

Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults

Cancer-related pain is complex and multi-dimensional but the mainstay of cancer pain management has predominately used a biomedical approach. There is a need for non-pharmacological and innovative approaches. Transcutaneous Electric Nerve Stimulation (TENS) may have a role for a significant number of patients but the effectiveness of TENS is currently unknown.

The aim of this systematic review was to determine the effectiveness of TENS for cancer-related pain in adults. Only two RCTs met the eligibility criteria (64 participants). These studies were heterogeneous with respect to study population, sample size, study design, methodological quality, mode of TENS, treatment duration, method of administration and outcome measures used. In one RCT, there were no significant differences between TENS and placebo in women with chronic pain secondary to breast cancer treatment. In the other RCT, there were no significant differences between acupuncture-type TENS and sham in palliative care patients; this study was underpowered.

The results of this systematic review are inconclusive due to a lack of suitable RCTs. Large multi-centre RCTs are required to assess the value of TENS in the management of cancer-related pain in adults.

- Hurlow A, Bennett MI, Robb KA, Johnson MI, Simpson KJ, Oxberry SG. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD006276. DOI: 10.1002/14651858.CD006276.pub3.

Further references:

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Immunodiagnostic Tests and Immunotherapy (16/16)

Further information:

Recently, the recognition that chronic inflammation in the tumor microenvironment promotes tumor growth and survival during different stages of breast cancer development has led to the development of novel immunotherapies. Several immunotherapeutic strategies have been studied both preclinically and clinically and already have been shown to enhance the efficacy of conventional treatment modalities. Therefore, therapies targeting the immune system may represent a promising next-generation approach for the treatment of breast cancers.

A prospective case series was published by Adams et al (2012) to evaluate the local tumor response rate of breast cancer skin metastases treated with topical imiquimod, applied 5 d/wk for 8 weeks. Ten patients were enrolled. Two patients achieved a partial response. Responders showed histologic tumor regression with evidence of an immune-mediated response, showed by changes in the tumor lymphocytic infiltrate and locally produced cytokines.

Dendritic cell intradermal vaccination

In a recent paper from China (Qi et al, 2012) Dendritic cell (DC) vaccines were generated from CD14+ precursors pulsed with autologous tumor lysates. DCs were matured with defined factors that induced surface marker and cytokine production. Individuals were immunized intradermally four times. Overall survival and disease progression rates were compared with those of contemporaneous patients who were not administered DC vaccines. There was no difference in overall survival between the patients with and without DC vaccine. The 3-year progression-free survival was significantly prolonged: 76.9% versus 31.0% (with vs. without DC vaccine, $p < 0.05$). The authors concluded that their findings strongly suggest that tumor lysate-pulsed DCs provide a standardized and widely applicable source of breast cancer antigens that are very effective in evoking anti-breast cancer immune responses.

Recently, quite a number of preliminary clinical trials have been evaluated and published reporting on immunotherapeutic interventions yielding promising early results. In this context, Montero et al (2012) reported on the addition of NOV-002 (a formulation of disodium glutathione disulfide) to chemotherapy, which has been shown to increase anti-tumor efficacy in animal models and some early phase oncology trials. Concurrent NOV-002 resulted in 38% pCR rate for AC → T chemotherapy higher than previously reported e.g. in the B27 or the Geparduo trials.

This and other early indications of efficacy do not at all allow general recommendation, however they show, that further evaluation in the context of randomised trials should be actively supported.

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