

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Herausgegeben von der Kommission Mamma
(vertreten durch: Anton Scharl)
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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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How to Use these Slides

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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“)
- 25) Gynecological Issues in Breast Cancer Patients (Gynäkologische Probleme bei Mammakarzinompatientinnen)

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Oxford Levels of Evidence (LOE)

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)

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or 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
Erythropoetin
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 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

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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.**
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Potential Conflicts of Interest (COI) 2014-2015

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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:

American Diagnostica, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Chugai, Eisai, Fresenius Biotech, Genomic Health, GlaxoSmithKline, Johnson&Johnson, Luisenkrankenhaus, MCI München, medac, Medigene, Merck, MSD, Myriad Genetics, Nanostring, NeoDynamics, Novartis, Onkozert, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi-Aventis, Sividon Diagnostics, Teva, Willex, Zeiss.

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Options for Primary Prevention: Modifiable Lifestyle Factors

Prevention

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- **Version 2011: Gerber / Thomssen**
- **Version 2012–14:**
Dall / Diel / Maass / Mundhenke
- **Version 2015:**
Gerber / Mundhenke

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Further
Information

References

Non-modifiable Risk Factors for Breast Cancer

- **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 (risk increase))**

Reproductive risk factors

- **Lower number of births or no pregnancy**
- **Higher age at first full term delivery**

Modifiable Risk Factors for Breast Cancer

- **Less breast feeding**
- **BMI < 18.5 and > 25 and especially > 40 (obesity)**
- **Diabetes mellitus Type II**
- **Food content**
- **Steroid hormone therapy**
 - Recent oral contraceptive use
 - Hormone therapy in postmenopausal women
- **Alcohol intake**
- **Smoking**
- **Light exposure at night (night shifts)**
- **Low physical activity**
- **Toxic agents in fetal and early childhood development (DES, polyfluoroalkyls)**

Prevention by Changing Pregnancy Related Factors

**Oxford / AGO
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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Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

Oxford / AGO
LoE / GR

- **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** 2b B ++
(reduction of breast cancer incidence and mortality)

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Prevention by Changing Lifestyle

Factors: Diet

Oxford / AGO
LoE / GR

Preference of a healthy diet

2b B +

Dietary components

- Fat reduced food (unsaturated > saturated fatty acids)
- Reduced consumption of red meat
- Supplementation of vitamins, minerals, tracer elements
- Vitamin D substitution for prevention
- Vegetables / fruits
- Phytoestrogens / Soya
- Fiber containing food

2a B +

2a B +

2a B -

3a B +/-

2a B +/-*

2a B +/-

1b A +

* Recommended as a part of healthy nutrition

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: Smoking

Oxford / AGO
LoE / GR

- **Never smoking reduces risk of breast cancer**
(~ 15-24% reduction of lifetime risk) **2a B ++**
- **Young women smoking have a 60% increased risk of bc, when smoking > 10 years before the first childbirth (vs. never smokers)**

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

Oxford / AGO
LoE / GR

- **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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Prevention

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 +

Further
Information

References

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(–)

Options for Primary Prevention: Modifiable Lifestyle Factors (2/13)

Further information and references:

Screened data bases:

Pubmed 2005 - 2014, ASCO 2012 – 2014, SABCS 2012 – 2014, Cochrane data base (2014)

Screened guidelines:

NCI (National Cancer Institute , 2014): <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2014)

<http://www.asco.org/ASCO/Quality+Care+%26+Guidelines/Practice+Guidelines/Clinical+Practice+Guidelines/Breast+Cancer>.

CMA (Canadian Medical Association , 2014): <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

NCCN (National Comprehensive Cancer Network , 2014):

http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (download 13. JAN. 2015)

Non Modifiable Risk Factors for Breast Cancer (3/13)

No further information

References:

1. Modified from American Cancer Society 2014 (<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>) downloaded 01.01.2015)
2. Ritte et al.: Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer 2013 Dec 9;13:584.
3. Collaborative Group on Hormonal Factors in Breast Cancer: Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141-51.

Modifiable Risk Factors for Breast Cancer Risk (4/13)

No further information

References:

1. Modified from American Cancer Society 2010 (<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>, last revised 31.12.2013)
2. Gaudet MM et al: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013 Apr 17;105(8):515-25.

Prevention by Changing Pregnancy Related Factors (5/13)

No further information

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: 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
4. Martin RM: Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst. 2005;97:1446-57.
5. Li CI: Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20-44 years of age. Breast Cancer Res Treat. 2013;137:579-87.

Prevention by Changing Life Style Factors: Body Mass Index / Diet (6/13)

No further information

References:

1. Simpson ER: Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013 Nov 26;51(3):T51-9.
2. World Cancer Research Fund and American Institute for Cancer Research: Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC, AICR, 2007.
3. Cheraghi Z: Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7(12):e51446. doi:
4. 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
5. Chan DS: Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014 Oct;25(10):1901-14.
6. Brinton LA: Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst. 2014 Mar;106(3):djt465.

Prevention by Changing Life Style Factors: Diet (7/13)

No further information

References:

1. Trichopoulou A: Conformity to traditional Mediterranean diet and breast cancer risk in the Greek EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. Am J Clin Nutr. 2010 Sep;92(3):620-5.
2. Brennan SF: Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010 May;91(5):1294-302.
3. 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.
4. Zamora-Ros R: Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res Treat. 2013 May;139(1):163-76.
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7. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D., Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013 Jun 27;346:f3706.
8. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC., Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. BMJ. 2014 Jun 10;348:g3437

Prevention by Modifying Life Style Risk Factors: Alcohol (8/13)

No further information

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. Bagnardi V: Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2014 Nov 25. doi: 10.1038/bjc.2014.579. [Epub ahead of print]
3. Li CI: Alcohol Consumption and Risk of Postmenopausal Breast Cancer by Subtype: The Women's Health Initiative Observational Study. J Natl Cancer Inst 2010;102:1422–1431
4. Suzuki R: Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis of epidemiological studies. Int J Cancer. 2008 Apr 15;122(8):1832-41.
5. McDonald JA: Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. Curr Breast Cancer Rep. 2013 Sep;5(3).

Prevention by Modifying Life Style Risk Factors: Smoking (9/13)

No further information

References:

1. Dossus L: Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer. 2014 Apr 15;134(8):1871-88.
2. Gaudet MM: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013 Apr 17;105(8):515-25
3. Bjerkaas E: Smoking duration before first childbirth: an emerging risk factor for breast cancer? Results from 302,865 Norwegian women. Cancer Causes Control. 2013 Jul;24(7):1347-56.

Prevention by Modifying Life Style Risk Factors: Physical Activity (10/13)

No further information

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: review of the epidemiologic evidence and biologic mechanisms. Recent Results Cancer Res. 2011;188:125-39.
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.
5. Chlebowski RT: Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013 Aug;22 Suppl 2:S30-7.
6. Wu Y: Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2013 Feb;137(3):869-82.

Prevention by Modifying Life Style Risk Factors: Hormone Therapy in Postmenopausal Women (11/13)

No further information

References:

1. Chlebowski RT: Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA (2010) 304: 1684–1692
2. Beral V.: Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362: 419 – 27.
3. Reeves GK: Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol (2006) 7: 910–918.
4. Chlebowski RT: Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA (2003) 289: 3243–3253.
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7. Manson JE: 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.
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Prevention: Hormone (EGC) in der Post-MP (12/13)

No further information

No references

Prevention by Modifying Life Style Risk Factors: Oral contraception (13/13)

No further information

References:

1. Cibula D.:Hormonal contraception and risk of cancer. Human Reproduction Update, Vol.16, No.6 pp. 631–650, 2010
2. Gierisch JM: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.
3. 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.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Risk and Prevention

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➤ Versions 2003–2014:

**Schmutzler with Albert / Blohmer / Fehm /
Kiechle / Maass / Mundhenke / Rody /
Thomssen**

➤ Version 2015:

Schmutzler / Schmidt

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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

BRCA1/2 Testing in Patients with TNBC (irrespective of family history)

BRCA1/2 testing in patients with TNBC if an impact on treatment decisions is anticipated

**Oxford / AGO
LoE / GR**

Regardless of age *

3b C +

*** Study participation recommended**

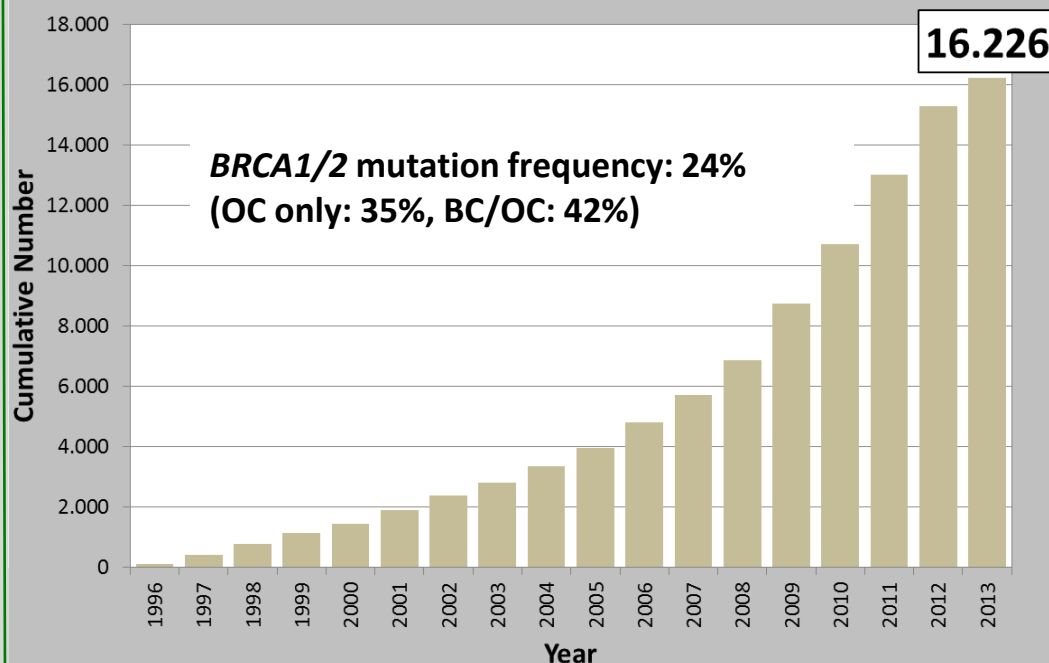
*** The rate of BRCA 1/ 2 mutation is decreasing with increasing age**

Recruitment of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)

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18.875 in 2014; exp. +3.000 new families in 2015



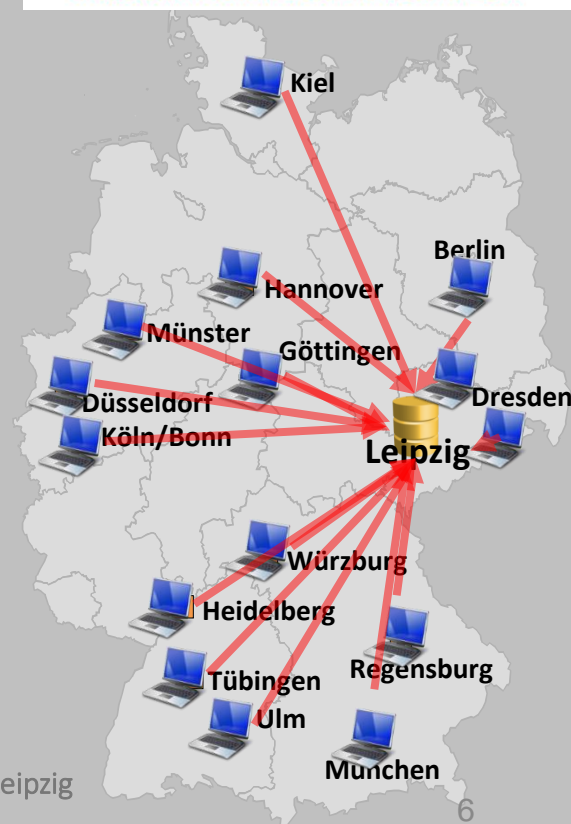
- since 1996, 15 centres
- national database (IMISE*, Leipzig)
- national DNA-biobank (center Cologne)

*Institute for Medical Genetics, Statistics and Epidemiology, Leipzig



**DEUTSCHES
KONSORTIUM**
für familiären Brust-
und Eierstockkrebs

unterstützt durch die Deutsche Krebshilfe e.V.



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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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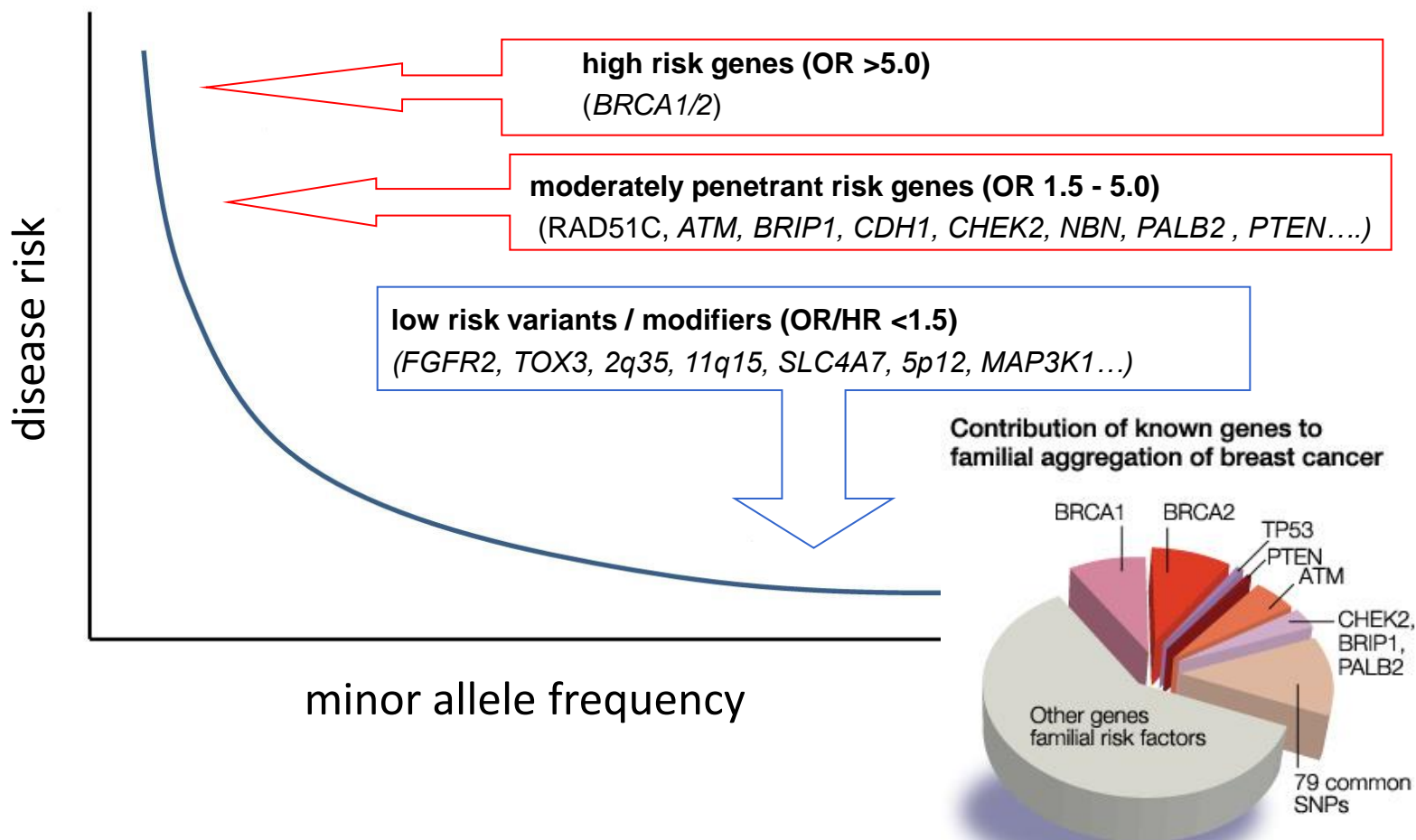
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State of the Art

Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity



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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Recommendation: genetic counselling: GCP

Third Moderate to High Risk Gene Identified within the GC-HBOC

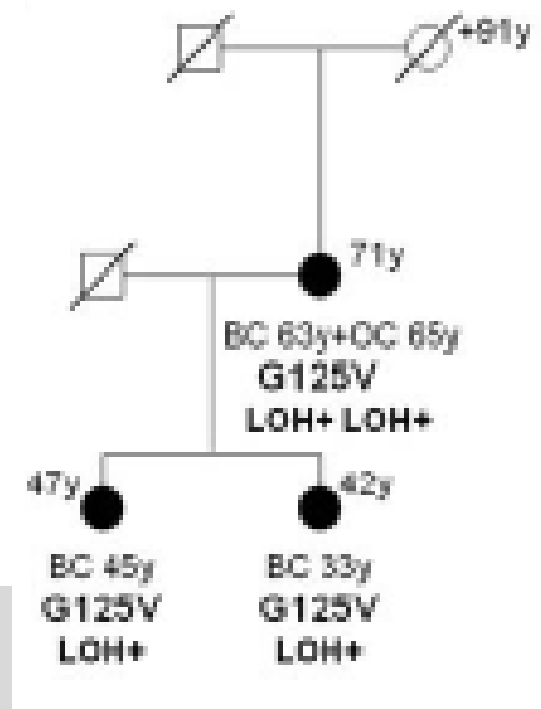
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Germ-line mutations in breast and ovarian cancer pedigrees establish
RAD51C as a human cancer susceptibility gene

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. Schmutzler^{3*}, Helmut Hanenberg^{2,15*}



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References

- 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%**)

Commercially 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

TruRisk™ BC/OC Gene Panel (34 genes)

by the German Consortium GC-HBOC

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ATM core gene	BRCA1 core gene	BRCA2 core gene	CDH1 core gene	CHEK2 core gene	NBN core gene	PALB2 core gene	RAD51C core gene
RAD51D core gene	TP53 core gene	MLH1 Lynch syndrome	MSH2 Lynch syndrome	MSH6 Lynch syndrome	PMS2 Lynch syndrome	ENIGMA #1	ENIGMA #2
ENIGMA #3	ENIGMA #4	ENIGMA #5	ENIGMA #6	ENIGMA #7	ENIGMA #8	ENIGMA #9	ENIGMA #10
ENIGMA #11	ENIGMA #12	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC
candidate GC-HBOC	candidate GC-HBOC						

Gene selection:

- 10 BC/OC 'core genes'** (sufficient data for genetic counseling)
- 4 HNPCC genes** (~1% of unselected OC cases show truncating mutations; Song et al., 2014)
- 12 BC/OC 'research genes'** (validation in cooperation with the ENIGMA consortium)
- 8 candidate BC/OC genes** (GC-HBOC, unpublished)

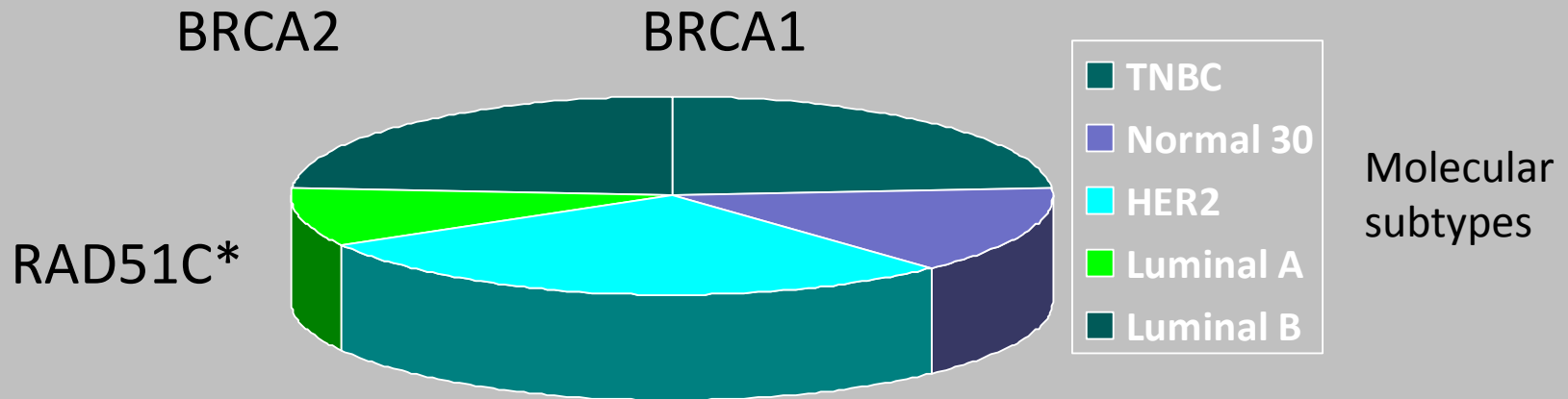
Strategy:

➤ Validation in large cohort, constant expansion and improvement

Clinical Implication: Genotype/Phenotype

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*Meindl et al. Nat. Genet 2010

Gevensleben et al. submitted

➤ Genotype determines not only disease penetrance but phenotype and clinical disease course

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References

Genetically Defined Subtypes are Distinct Tumor Entities

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

- Disease penetrance?
- 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**

VUS: Problems and Questions

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- 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 yet

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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

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.

- Clinical genetic testing for *RAD51C*; *CHEK2* and/or other moderate risk genes, e.g. gene panels
- Clinical genetic testing for low risk variants
- Referral to centres of the GC-HBOC or cooperating centres

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2b	B	-
3b	D	--
5	D	++

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)**

1a A ++

2b B +

2a B ++

Surveillance Program for Women with Deleterious BRCA-mutations*

**Oxford / AGO
LoE / GR**

Multimodal intensive surveillance program lifelong

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 (until ACR1)	≥25 years	annual			
➤ For mortality reduction (10 year survival)			4	C	+

***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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Surgical Prevention

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- **Unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors**

2a

B +*

Surgical Prevention for Healthy BRCA1/2 Mutation Carriers

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LoE / GR

- **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

***Study participation recommended**

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

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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**

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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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.

	<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)

Therapy of BRCA1/2-associated Breast Cancer+

Limited prospective cohort studies with short follow-up time

➤ **Breast conserving therapy:**

➤ **Adequate local tumor control (10 years observation)**

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2a B +

➤ **Systemic therapy according to sporadic breast cancer**

3a B +

➤ **BRCA1 mutation status is predictive for chemotherapy response**

3b B +

➤ **Carboplatin (vs. Docetaxel) in MBC**

2b^a B +

➤ **PARP inhibitor in breast cancer**

2b D +/-*

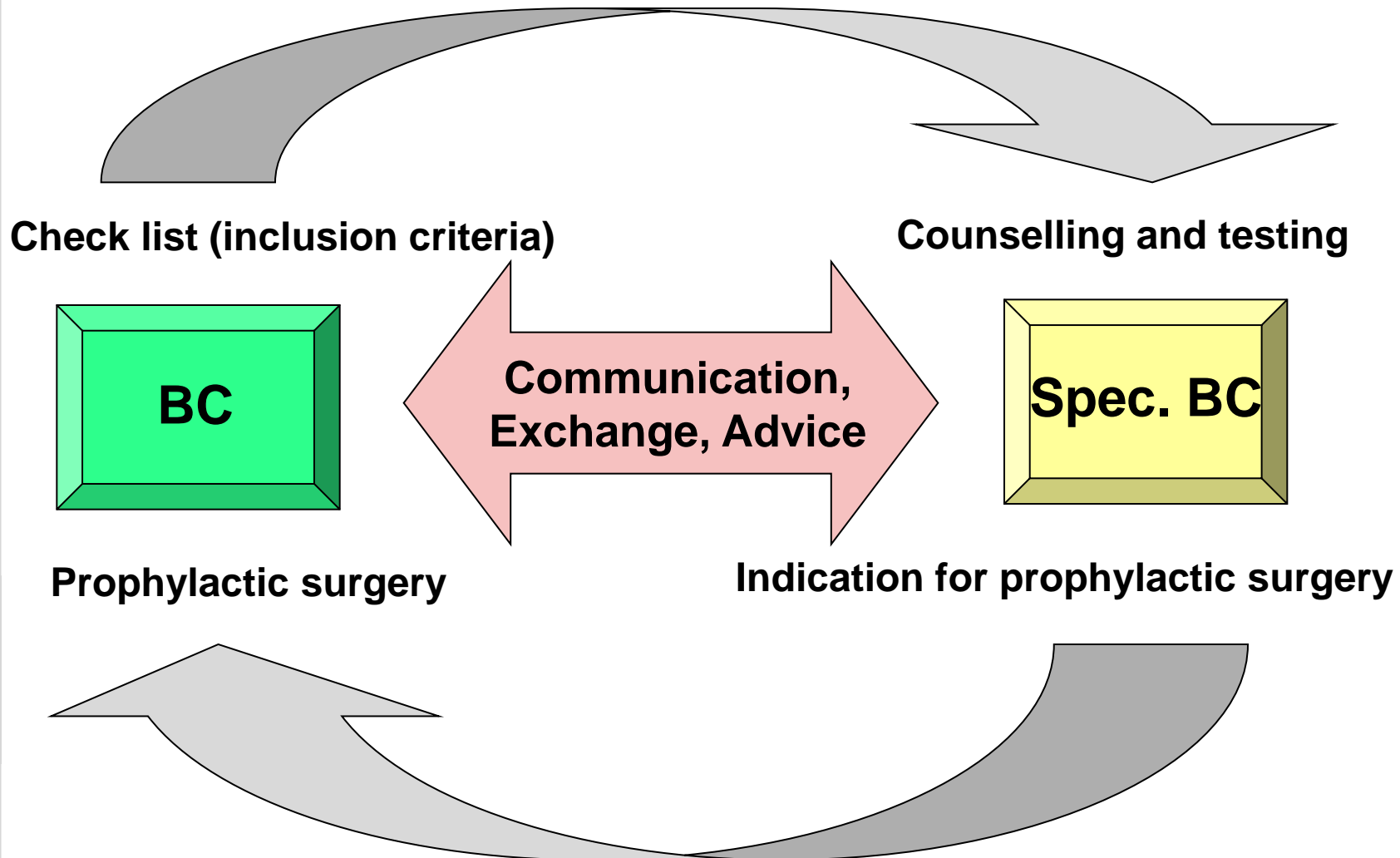
+ Overall prognosis has to be considered

***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

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- | | | | |
|---|-----------|----------|----------|
| ➤ 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 (2/32)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references

Principles in Prevention (3/32)

No further information

No references

Who Should be Tested for BRCA1/2 Mutations? (4/32)

No further information

References:

1. Meindl et al.: Comprehensive analysis of 989 patients with breast and ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. Int. J Cancer 2002: 97:472-480
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%.

BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (5/32)

Further information:

TED poll:

N=5 „as predictive marker“

N=21 „impact“

N=3, omit

N=9 ++

N=21 +

References:

Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer.

1. **Couch** FJ, Hart SN, Sharma P, Toland AE, Wang X, Miron P, Olson JE, Godwin AK, Pankratz VS, Olswold C, Slettedahl S, Hallberg E, Guidugli L, Davila JJ, Beckmann MW, Janni W, Rack B, Ekici AB, Slamon DJ, Konstantopoulou I, Fostira F, Vratimos A, Fountzilas G, Peltari LM, Tapper WJ, Durcan L, Cross SS, Pilarski R, Shapiro CL, Klemp J, Yao S, Garber J, Cox A, Brauch H, Ambrosone C, Nevanlinna H, Yannoukakos D, Slager SL, Vachon CM, Eccles DM, **Fasching** PA. J Clin Oncol. 2015 Feb 1;33(4):304-11. doi: 10.1200/JCO.2014.57.1414. Epub 2014 Dec 1.

Recruitment of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) up to 2013 (6/32)

No further information

No references

Suggested Use of a Screening Checklist (7/32)

No further information

No references

State of the Art: Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (8/32)

No further information

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No further information

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Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction (11/32)

No further information

No references

TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC (12/32)

No further information

No references

Clinical Implication:Genotype/Phenotype (13/32)

No further information

No references

Genetically Defined Subtypes are Distinct Tumor Entities (14/32)

No further information

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VUS: Problems and Questions (15/32)

No further information

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No further information

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Low Risk Variants as Modifier (17/32)

No further information

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No further information

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No further information

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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)

Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease (23/32)

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Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (25/32)

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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)

Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (26/32)

No further information

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No further information

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Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive) (28/32)

No further information

No references

Therapy of BRCA1/2-associated Breast Cancer+ (29/32)

Further information:

TED poll:

Caboplatin (vs Docetaxel): 3 ++, 17 +

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Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (30/32)

No further information

No references

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No further information

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Risk Reduction for Ipsi- and Contralateral Breast Cancer (32/32)

Further information:

Large RCTs have proven a risk reduction of breast cancer by Tamoxifen, aromatase inhibitors and the combination of GnRHa plus Tamoxifen

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 2005–2014:

**Albert / Blohmer / Fersis /
Junkermann / Maass / Scharl /
Schreer**

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Schreer / Albert

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Early Detection Mammography

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

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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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Early Detection Sonography

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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 ++

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References

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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**FORSCHEN
LEHREN
HEILEN**

* May increase breast awareness

Assessment of Breast Symptoms or Lesions

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➤ **Clinical examination**

➤ **Mammography**

➤ **Additional Tomosynthesis
(vs spot compression)**

➤ **Sonography**

➤ **Elastography (shear-wave)**

➤ **Automated 3D-sonography**

➤ **MRI***

➤ **Minimally invasive biopsy**

**Oxford / AGO
LOE / GR**

3b B ++

1b A ++

2b B +

2b B ++

2b B +

3b B +/-

2b B +/-

1c A ++

* If clinical examination, mammography and
sonography do not allow a definite diagnosis

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References

**FORSCHEN
LEHREN
HEILEN**

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

- **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)]**

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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Further
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References

MRI Screening in Women with High Familiar Risk

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				MRT		Mammographie	
Autor	Hochrisiko / Mutation	Anzahl Frauen	Anzahl Karzinome	Sensitivität (%)	Spezifität (%)	Sensitivität (%)	Spezifität (%)
Kriege 2004	M	1909	50	80	90	33	95
Warner 2004	M	236	22	77	95	36	99
Hagen 2004	M	491	25	86	-	50	-
Leach 2005	H / M	649	35	94	77	40	93
Riedl 2007	H / M	327	28	50	98	85,7	92
Kuhl 2010	H / M	687	27	93	98,4	33	99,1
Rijnsburger 2010	M	594	97	77,4	89,7	41	-
Sardanelli 2011	H / M	501	52	91	97	50	-
Passaperuma 2012	M	496	57	90	97	19	97
Gareth 2014	H / M	649	139	93	63	60	-

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Information

References

FORSCHEN
LEHREN
HEILEN

Prospective study results for MRI screening in women with high familiar risk (H) and mutation carriers (M)

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%

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 (2/15)

Further information and references:

Screened data bases:

- Pubmed 2009 - 2014
- ASCO 2009 - 2014
- Cochrane 2009 - 2014
- Medline 2009 - 2014
- GIN 2009 - 2014

Guidelines:

- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

Early Detection – Mammography (3/15)

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.

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%.”

Data from observational studies and registries:

The EUROSCREEN 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 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”.

Since 2006 mammography screening is offered to women age 50-69 in Germany within a population-based organised quality assured program in accordance with the European Guidelines for Quality Assurance in Mammography Screening.

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Breast Cancer Mortality Reduction (4/15)

No further information

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Mammography Screening Women 40–49 years (5/15)

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.

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 (6/15)

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. Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination.

The arguments against ultrasound use as stand alone screening modality 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 (7/15)

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 (8/15)

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.

Digital breast tomosynthesis allows an increased breast cancer detection rate and its use is recommended for screening centers in population-based trials. Shear wave elastography (SWE) is a promising adjunct to greyscale ultrasound in differentiating benign from malignant breast masses (improved specificity of breast US mass assessment without loss of sensitivity thus reducing the need for core biopsy by downstaging US-BIRADS III and IVa lesions). Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination.

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 and Staging (9/15)

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 both invasive and non- 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 long time 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), but considering the present evidence no general recommendation can be given for preoperative MRI in patients before breast conservation.

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.

Preoperative ultrasound of the axilla and guided lymphnode biopsy prevent completion axillary lymphnode dissection in breast cancer. Elastography of lymph nodes might add prognostic information additional to that provided by conventional preoperative tumor assessment and staging. A general recommendation for the use of lymph node elastography cannot be given as data on quality assurance is lacking.

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MRI: Preoperative Staging (10/15)

No further information

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MRI Preoperative Staging in Lobular Invasive Breast Cancer (11/15)

No further information

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MRI Screening (High-risk) – Benefit (12/15)

No further information

No references

MRI Screening in Women with High Familial Risk (13/15)

Further information:

Six prospective multicentre studies and further systematic reviews showed that additional use of MRI increased the sensitivity significantly and that cancers could be detected at a better stage. Overall sensitivity levels ranged from 77% - 100%. About 33% of malignancies were detected by MRI alone, about 11% by mammography alone and only 3% by ultrasound alone. Therefore MRI should be the first imaging method used for intensified screening in high-risk women. It is still unclear whether early detection by MRI will translate into improved disease-free and overall survival.

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MRI Screening (High Risk) Problems (14/15)

No further information

No references

MRI and DCIS (15/15)

No further information

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Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Pathology

Pathology

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- **Versionen 2004–2014:**
**Costa / Fehm / Friedrichs / Huober /
Kreipe / Lück / Sinn / Thomssen**
- **Version 2015:**
Sinn / Friedrichs

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General Principles for Histopathologic Examination of Breast Cancer Specimens

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- **Any statement in the histological report should reflect its clinical significance**
- **The terminology used is chosen according to current national guidelines and international classifications**
- **Quality control measures are required in all areas of diagnostic pathology**

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Preanalytics: Fixation

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- **Minimize time to fixation (cold ischemia time)**
- **Minimal fixation time of 6 hours for optimal antigen preservation**
- **Optimal fixation time 6 - 72 h for core biopsies**
- **Optimal fixation time for resection specimens: 12 - 72 h**
- **Use of neutral buffered formalin**

Oxford / AGO
LoE / GR

5 D ++

5 D ++

5 D ++

5 D ++

5 D ++

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Use of Fine Needle Aspiration Cytology*

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- **Nipple secretion**
- **Tumor**
- **Cyst**
- **Lymph node**

Oxford / LoE / GR	AGO
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5	D	+
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5	D	-
---	---	---

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

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

* **Ultrasound-guided core biopsy recommended**

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Workup: Macroscopy and Specimen Radiography

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- **Consideration of preoperative imaging results (e.g. multifocality, intraductal component, adjacent structures) for sampling and documentation**
- **Routine documentation of macroscopic findings by using diagrams or macro image, with relation to topography**
- **Specimen radiography for non-palpable lesions and microcalcifications**

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Workup: Core Needle Biopsies (US-guided or stereotactic)

Oxford / AGO
LoE / GR

- | | | | |
|--|-----------|----------|-----------|
| ➤ Routine workup in step sections
(14G: 3 sections / 11G, 8G: 6–8 sections) | 5 | D | ++ |
| ➤ Correlation with imaging (density,
calcifications), use of B-classification | 1b | B | ++ |
| ➤ Frozen section diagnosis on core biopsies | 5 | D | -- |
| ➤ Routine evaluation of ER/PgR and HER2
status | 3b | C | ++ |
| ➤ Turn-around time < 24 h (histology) | 5 | D | + |

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Workup: Breast-Conserving Specimens

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: 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)**

5 D ++

5 D ++

5 D ++

5 D ++

Workup: Sentinel Node Biopsy

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	Oxford LoE / GR	/	AGO
➤ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
➤ Cytokeratin immunohistochemistry			
- When suspicious, to detect micromet.	2b	B	++
- As a routine procedure	5	D	+/-
➤ Frozen section (invasive Ca.)			
- If clinical consequence	5	D	+
- If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BCT)	5	D	+/-
➤ Imprint cytology instead of, or in addition to frozen section	3b	C	+/-
➤ RT-PCR for epithelial genes	4	D	-
- OSNA	3b	B	-

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	+

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Reporting: Histologic Tumor Type

Oxford
LoE / GR

AGO

3b C

++

➤ Histologic tumor typing according to WHO- Classification, (4th ed., 2012)

- **Partial special differentiation:**
 - > 50% NST component
 - and < 50% special tumor type (minor component)
- **Mixed differentiation:**
 - > 50% special tumor type
 - and < 50% NST component
 - Example: mucinous breast cancer, mixed type
- **Pure types:**
 - > 90% special tumor type
 - Examples: tubular or cribriform Ca.

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Reporting: Grade of Malignancy

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		Oxford LoE / GR	AGO
➤ Use of Nottingham grading system (Elston & Ellis 1991) for all types of invasive breast cancer	5	D	++
➤ In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used	5	D	++
➤ Grading of DCIS according to WHO-Classification, (4th ed., 2012)	5	D	++
➤ Reporting of tumor grading in numeric form (e.g. G3)	5	D	++

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Reporting: Tumor Size and Total Extent of Tumor

Oxford
LoE / GR

AGO

- **Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results**
- **Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality**
- **Reporting of size of noninvasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2x invasive Ca)**

5 D ++

5 D ++

5 D ++

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Reporting: pTNM

Oxford
LoE / GR

AGO

5 D ++

➤ Use of current UICC classification (7th ed.)

pT 1 - 3: Invasive tumor size (largest focus in case of multiplicity)

pT4: Invasion of dermis alone does not qualify as pT4. Criteria for pT4a/b/c/d must be met.

pT4d: Negative skin biopsy does not rule out pT4d (inflammatory carcinoma).

pM: pM1 indicates any non-regional disease, except 2nd primary contralaterally. Use of MX is not recommended.

Reporting: Margins of Resection and R-Classification

Oxford
LoE / GR

AGO

- | | Oxford
LoE / GR | AGO |
|---|--------------------|-----------|
| ➤ Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm) | 5 D | ++ |
| ➤ Reporting of minimal distance to resection margin and topography thereof | 5 D | ++ |
| ➤ R-Classification | 5 D | ++ |

R0: No residual tumor

**R1: Microscopic invasive or noninvasive
Carcinoma involving resection margin**

**RX: Presence of residual tumour cannot be
assessed (e.g. tumor in multiple specimens)**

Reporting: Lymphovascular invasion

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	Oxford LoE / GR	AGO
➤ L1: Lymphovascular invasion L0: No lymphovascular invasion	5 D	++
➤ IHC for evaluation of lymphovascular invasion	3b C	-
➤ Differentiation of peritumoral and extensive lymphovascular invasion	3b C	++
➤ Reporting of venous invasion (V0/V1) optional, prognostic significance not established	5 D	+

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Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

Oxford
LoE / GR

AGO

5 D +/-

- **Identification of tumors with predominant lymphocytic infiltrate (> 50%) in tumor stroma (according to Salgado et al.*)**

Consider only lymphocytic infiltrate in tumor stroma and at the invasion front

Do not consider central fibrosis and necrotic areas

Reort average of lymphocytic infiltrate as percentage

*Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Annals of Oncology*

Reporting: 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	++
➤ pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded	2b	D	+
➤ Use of IHC to identify tumor residues	4	D	+/-
➤ Reporting of ypTN after therapy	5	D	++

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Special studies: ER-Testing by IHC

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	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 (0 - 3)	4	D	+
➤ Allred Score (0 - 8), Remmele Score (0 - 12)	4	D	+
➤ Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy	5	D	+

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Special studies: PgR-Testing by IHC

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LoE / GR

- | | | | |
|--|----|---|----|
| ➤ Immunohistochemical detection on paraffin embedded (FFPE) tissue | 1a | A | ++ |
| ➤ Reporting percentage of pos. tumor nuclei (pos. if $\geq 10\%$) | 1a | A | ++ |
| ➤ Staining intensity of pos. tumor nuclei (0 - 3) | 4 | D | + |
| ➤ Allred Score (0 - 8), Remmele Score (0 - 12) | 4 | D | + |

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Additional special studies: Molecular analysis of ER/PgR status

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LoE / GR

- Evaluation of hormone receptors using validated gene expression test kits
- Evaluation of hormone receptor by RNA-sequencing
- Use of molecular receptor analysis for subtyping

3b A +/-

5 D -

3b A +

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Special studies: HER2 Testing

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➤ Reporting of immunohistochemistry (IHC):	1a	A	++
- 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)			
➤ Reporting of single-color In-Situ-Hybridisation (ISH):	3a	C	++
- HER2+ if signal counts ≥6 in at least 20 cohesive cells, negative if signal counts < 4 signals/nucleus			
➤ Reporting of dual-color ISH:	3a	C	++
- positive if signal ratio HER2:CEP17 ≥ 2,0 and/or HER2-signals ≥6			
➤ Equivocal results (2+ IHC, ≥4 - <6 HER2 signals ISH):	3a	C	++
Retest using other method and/or tissue block			
➤ Validation of immunohistochemistry on core biopsies	5	D	++

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

Additional Special Studies: Molecular Analysis of HER2 Status

Oxford / AGO
LoE / GR

- | | | |
|--|-------------|------------|
| ➤ Therapy decisions should be based on IHC and ISH only | 1a A | ++ |
| ➤ Evaluation of HER2 durch using validated gene expression test kits | 3b B | +/- |
| ➤ Evaluation of HER2-amplification by RNA-sequencing | 5 D | - |
| ➤ Use of molecular HER2-testing for subtyping | 3b B | +/- |

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Special studies: Evaluation of Ki-67 Score

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	Oxford LoE / GR	AGO
➤ Counting of tumor nuclei at the invasion front	5 D	++
➤ Consideration of weakly stained tumor nuclei	5 D	++
➤ Reporting of Ki-67 positive nuclei as percentage	5 D	++
➤ Establishing of laboratory standards and cut-off values	5 D	++
➤ Use of image analysis for objective Ki-67 evaluation	5 D	+

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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Quality Assurance: Immunohistochemistry

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- **Use of automated staining platform**
- **Participation in ring trials**
- **Strict adherence and monitoring of requirements of preanalytics (fixation)**
- **Use of on-slide controls**
- **Plausibility controls (e.g. tumor type, grading)**

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References

Quality assurance: HER2-Status

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- **Continuous documentation of HER2 tests**
- **Quality goal: Rate of HER2-positivity: 15% - 20%**
- **Use of standardized and validated HER2 test kits**
- **Participation in ring trials**

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Further
Information

References

Quality Assurance: Reporting

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- **Responsibility of one or two pathologists with special expertise in breast pathology**
- **Regular interdisciplinary conferences with radiologic-pathologic correlation**
- **Participation in quality circles**

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Further
Information

References

Pathology (2/30)

Further information:

This chapter contains basic recommendations for routine procedures in pathology. It is not intended 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:

Screened data bases: PubMed 1970 – 2014

Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms.
Aktualisierung 2012
- NCCN Breast cancer V.I.2014Cochrane: Decision aids for risk communication update 2009
- 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

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General principles for Histopathologic Examination of Breast Cancer Specimens (3/30)

No further information

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Preanalytics: Fixation (4/30)

No further information

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Use of Fine Needle Aspiration Cytology (5/30)

No further information

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Workup: Macroscopy and Specimen Radiography (6/30)

No further information

References:

Clinical-pathological correlation diagnostics

1. NHS (2005) Pathology Reporting of Breast Disease. IA Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology
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Workup: Core Needle Biopsies (US-guided or stereotactic) (7/30)

No further information

References:

Statement: Routine workup in step sections

1. Krainick-Strobel U, Hahn M, Duda VF, Paepke S, Peisker U, Petrich S, Scheler P, Schwarz-Bocker U, Sinn HP, Heywang-Köbrunner 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
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Statement: Correlation with imaging

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Statement: Frozen section diagnosis on core biopsies

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

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Statement: Turn-around time < 24h

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

Workup of Breast-Conserving Specimens (8/30)

No further information

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.
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Workup of Mastectomy Specimens (9/30)

No further information

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.
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Evaluation of Sentinel Node Biopsy (10/30)

No further information

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Statement: Evaluation of sentinel node biopsy:

1. 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

Statement: Full workup using step sections of $\geq 500 \mu\text{m}$ on paraffin embedded tissue

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2. 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

Statement: Frozen section

1. Grabau DA, Rank F, Friis E (2005). Intraoperative frozen section examination of axillary sentinel lymph nodes in breast cancer. APMIS. 113:7-12

Statement: Imprint cytology instead or in addition of frozen section

2. Layfield et al. Intraoperative assessment of sentinel lymph nodes in breast cancer. *The British journal of surgery* (2011) vol. 98 (1) pp. 4-17
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Statement: RT-PCR for epithelial genes

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Indications for Immediate Pathological Analysis Including Frozen Sections (11/30)

No further information

References:

Statement: Sentinel node biopsy for invasive cancer

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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, Torrenge 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

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/>
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Statement: Lesions \geq 1 cm, without core biopsy

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Statement: Non-palpable lesions or lesions $<$ 1 cm

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.

Reporting: Histologic Tumor Type (12/30)

No further information

References:

WHO-Classifikation

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Reporting: Grade of Malignancy (13/30)

No further information

References:

Grading

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2. Lakhani SR, Ellis I, Schnitt S et al. (2012) WHO Classification of Tumours of the Breast. IARC Press, Lyon
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Grading of invasive lobular carcinoma

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No further information

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No further information

No references

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No further information

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Special studies: Evaluation of Ki-67 Score (26/30)

No further information

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Intrinsic Breast Cancer Types (27/30)

No further information

No references

Quality assurance: Immunohistochemistry (28/30)

No further information

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Quality assurance: HER2-Status (29/30)

No further information

No references

Quality assurance: Immunhistochemistry (30/30)

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

➤ **2002–2014:**

**Costa / Friedrichs / Gerber / Göhring /
Harbeck / Liedtke / Loibl / Mundhenke /
Nitz / Rody / Schaller / Schmidt /
Schmutzler / Schneeweiss / Simon /
Solomayer / Thomssen**

➤ **2015:**

Fersis / Janni

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”

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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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

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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	++
➤ Obesity (BMI >30kg/m ²)	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 *

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

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

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	Direct hybridization
Central lab	Yes	yes	no	no
Indication and population studied	prognostic N-/+, <61 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, 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	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	yes	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)	-	-

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\$ 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	-
➤ Multigene assay (EndoPredict®, Prosigna®, Oncotype DX®) \$ (N-/+, HR+, HER2-)	I	B	+*
➤ 70 gene signature (MammaPrint®), N0-1	II	C	+*
➤ 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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Neoadjuvant Systemic Therapy Response Prediction II

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Factor	LoE ₂₀₀₉	CTS	GR	AGO
➤ Multigensignatur e (Mammaprint, Endopredict Oncotyp Dx, PAM50 Prosigna^{\$})	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumour infiltrating lymphocytes	I	B	B	+/-
➤ <i>PIK3CA</i> mutation	II	B	B	+/-

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

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Predictive Factors – Endocrine Therapy

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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	+/-
➤ Obesity (BMI >30 kg/m ²)	2b	B	+/-

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

LoE₂₀₀₉

CTS

AGO

➤ Circulating tumor cells (CTC in blood, Cell Search[®])

- | Factor | LoE ₂₀₀₉ | CTS | AGO |
|---|---------------------|----------------|-----|
| ➤ Prognosis at baseline | I | B ^a | + |
| ➤ Early Response assessment (3w) | I | B | + |
| ➤ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype | I | A ^a | -* |

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* Study participation recommended

Prognostic and Predictive Factors (2/20)

Further information:

Data bases screened: Pubmed 2008 - 2015, ASCO 2003 – 20014, SABCS 2003 – 20014 , ECCO (n.d.), EBCC 2007 (n.d.).
Cochrane data base (n.d.)

Guidelines screened:

A. Goldhirsch 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) 1-18
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>

- ASCO 2007: Harris L et al. American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. J Clin Oncol. 2007 Nov 25 (33): 5287-5312

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1. Clark GM et al. Prognostic and predictive factors. In: Diseases of the breast, 2nd edition: Seiten 489-514. Harris JR, Lippmann ME, Morrow M, Osborne CK (Hrsg). Lippincott-Raven Publishers, Philadelphia 2000.
2. Graeff, H., Wilmanns, W., Jänicke, F., Sauer, H., Classen, S. (1997) Prognostische und therapierelevante Faktoren beim Mammakarzinom – Ergebnisse einer Konsensuskonferenz. In: Excerpta Oncologica. Prognostische und therapierelevante

Faktoren beim Mammakarzinom. Ergebnisse einer Konsensuskonferenz. Classen S, Graeff H, Jänicke F, Sauer H, Wilmanns W (Hrsg.), Novartis Pharma Verlag, Nürnberg, S. 135 - 158.

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 leukemia / MDS. Because of this, proper risk assessment is mandatory.

References:

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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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Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination (6/20)

No further information

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Revised Determination of Levels of Evidence Using Elements of Tumor Marker Studies (7/20)

No further information

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Requirements of a Marker-Based test to Reach Level IB Evidence (8/20)

No further information

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Prognostic Factors I in Early Breast Cancer (9/20)

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Statement: Obesity

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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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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-.

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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-.

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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.

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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)

Further information

The prognostic value of circulating tumor cells (CTC) in primary and metastatic breast cancer is subject of several publications. CTC detection helps to identify patients with increased risk for relapse. A number of trials showed that CTC can be used for treatment monitoring or direct treatment target. Nevertheless the role of CTC in breast cancer is still currently limited and further development in techniques will be pivotal in enhancing the broad applicability of CTCs and advancing the field of personalized breast cancer therapy.

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CTC

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Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)

Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

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- **Versions 2005–2014:**
**Albert / Audretsch / Brunnert / Fersis /
Friedrich / Gerber / Kreipe / Nitz / Rody /
Schreer / Sinn / Thomssen**
- **Version 2015:**
Kreipe / Thomssen

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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**
 - **Atypical papilloma, if incompletely removed**
 - **Radial scar, complex sclerosing lesion**

Major B3-Lesions and Prospektive Prediktive Value (PPV) for Malignancy in Resection

B3-Lesions:

~PPV

- | | |
|--|--------|
| ➤ Atypical ductal hyperplasia (ADH) | 40-50% |
| ➤ Lobular intraepithelial Neoplasia (LN/LIN) | 0-20% |
| ➤ Flat epithelial atypia (FEA) | 15% |
| ➤ Radial Scar | 3% |
| ➤ Complex sclerosing lesion | 3% |
| ➤ Papilloma without atypia | 0% |
| ➤ Cellular fibroepithelial tumors / phyllodes tumors | ? |

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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), atypical epithelial proliferation of ductal type
- 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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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

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

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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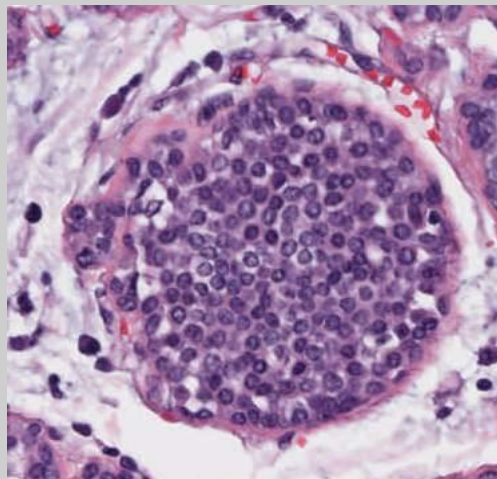
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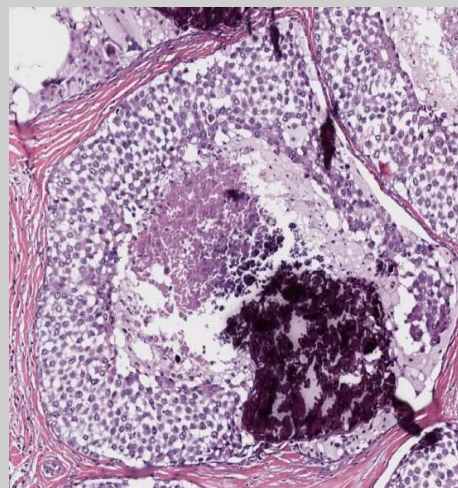
Variants of Lobular Neoplasia

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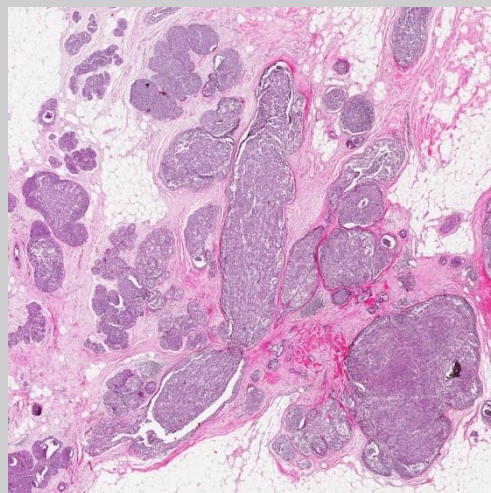
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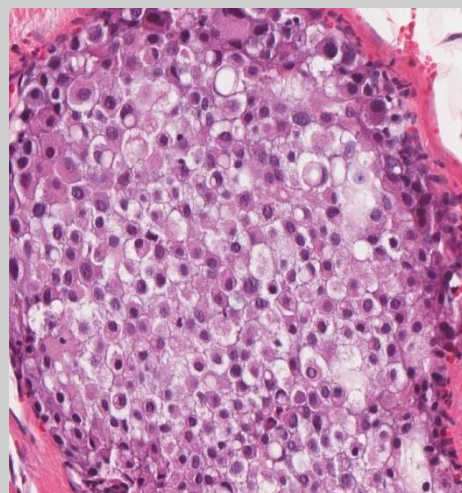
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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LCIN 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

* Ross DS. Am J Surg Pathol 2011 35: 750–6

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

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➤ **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

5 C +

➤ **FEA at margins in resection specimen:**

3b C ++

→ No further surgery, unless calcifications have not been completely removed

* Terminal ductal-lobular unit

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

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- **Papilloma without atypia in core needle or vacuum biopsies:**

→ no further therapy, when biopsy sufficiently representative (100 mm²) and no discordance to imaging

3a C ++

- **Papilloma with atypia in core needle or vacuum biopsies:**

→ open biopsy

3a C ++

Papilloma at resection margin:

→ no published 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

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3b C +

5a C +

➤ Radial scar / CSL at margins in resection specimen:

- No further surgery

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

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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)

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- **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 (Exemestan, Anastrozole)
for postmenopausal women** **1b A +/-**

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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Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen)

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
± LCIS	5.93	3.41	0.58	0.46-0.72
+ LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
+ ADH	10.42	2.55	0.25	0.10-0.52
5-year risk <2%	4.77	3.18	0.67	0.43-1.01
5 year risk > 5%	11.98	5.15	0.43	0.28-0.64
Relative 1.grade	6.47	3.48	0.54	0.34-0.83
> 3 relatives 1. grade	11.24	5.48	0.49	0.16-1.34
Fraktures	2.88	1.97	0.91	0.51-0.92
Endometriumcancer	0.68	2.24	3.28	1.87-6.03

Should only be offered to women with enhanced breast cancer risk (Gail $\geq 1,66\%$):

- LIN, ADH
- Family history of breast cancer

Should not be offered to women:

- With moderate risk > 50year of age Lebensjahr
- With enhanced risk for thrombembolism

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Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen, Side Effects)

**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)**

Incidence	RR	95% CI	AR je 1000*	NNT / NNH**
Breast cancer	0.73	0.58-0.91	15	68
Invasive carcinoma	0.74	0.58-0.94	12	81
Thrombembolism	1.72	1.27-2.36	14	73
Deep vein thrombosis leg	1.84	1.21-2.82	9	115
Headache	0.93	0.87-0.99	25	39
Gyneekological-/ vasomotoric symptoms	1.08	1.06-1.10	64	16
Chest pain	0.77	0.70-0.84	58	17

AR*:Absolute risik per 1000 women. NNT/NNH = number needed to treat or number needed to harm: shown are statistically signifikant associations for a follow-up-period of 96 month.**

Visvanathan K et al. JCO 2009;27:3235-3258.

Medical Prevention after Diagnosis of B3 Lesion (Raloxifen)

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
± LIN	3.76	3.89	1.03	0.81-1.33
+ LIN	9.83	9.61	0.98	0.58-1.63
± ADH	4.06	4.03	0.99	0.76-1.28
+ ADH	5.21	5.81	1.12	0.72-1.74

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Should only be offered to women with enhanced breast cancer risk :

(Gail $\geq 1,66\%$) or postmenopausal

Should not be offered to women:

- With moderate risk > 50year of age
- With enhanced risk for thrombembolism

Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors)

Inclusion criteria:

➤ IBIS.2:

- Prior ADH, ALH, or LCIS
Anastrozole: 154 (8.0%);
Placebo: 190 (9.7%)

Results for prior ALH, ADH, LCIS (HR AI vs Plac):

- Yes (7y-BC-risk 12.1%):
HR 0.31 (0.12–0.84)
- No (7y-BC-risk 4.9%):
HR 0.52 (0.31–0.78)

➤ MAP.3:

- Prior ADH, ALH, or LCIS:
Exemestane: 185 (8.1%);
Placebo: 188 (8.3%)

- Yes: HR=0.61 (0.20–1.82)
- No HR=0.26 (0.11–0.64)

Lesions of Uncertain Malignant Potential (B3) (2/25)

Further information and references:

Pubmed 2010-2015 (plus earlier publications if relevant):

Pubmed Search Strategies:

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])

Screened Guidelines:

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

National and international guidelines

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Pathology Reporting for Minimal Invasive Biopsies (3/25)

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 E. C. Working Group on breast screening pathology encompasses the heterogeneous B3 category.

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B3-Lesions (4/25)

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].

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Major B3-Lesions and Prospektive Prediktive Value (PPV) for Malignancy in Resection (5/25)

Further information:

In this category atypical intraductal hyperplasia (ADH), flat epithelial atypia (FEA), and lobular intraepithelial neoplasia (LN/LIN) are grouped together as lesions of uncertain biological behaviour. Besides these diagnoses papillomas, radial scar and phyllodes-tumour belong to the B3 group. In older studies approximately one-third of CNB results classified as B3 were malignant on excision, but the likelihood of malignancy varied substantially between specific lesion groups. Whereas cases may be selectively managed without surgery, the majority warrant excision biopsy (Rakha 2010, Houssami 2010). No clinical and radiologic findings and/or comprehensive evaluation of multiple histologic parameters on CNB specimen are distinctive enough to predict final classification of equivocal cellular fibroepithelial lesions. In recent years publications demonstrated a decline in PPV except for ADH. This is particularly obvious for LIN, which only rarely shows upgrade to higher lesions in resection when careful correlation between imaging and histology of CNB has been performed. Also papilloma without atypia usually shows no upgrade in resection. With regard to FEA different frequencies of upgrade to higher lesions are published. B3 lesions are diagnosed with less than 10% in mammography screening (6000 core biopsies, with central pathology). But 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 (Kreipe HH et al 2008).

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Management after Minimally Invasive Biopsy (6/25)

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.

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Atypical Ductal Hyperplasia (ADH) (7/25)

Further information:

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

Statement: indicator-/ precursor-lesion:

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).

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Strategy after Diagnosis of ADH (8/25)

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:

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Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH) (9/25)

No further information

References:

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Lobular Intraepithelial Neoplasia (LIN) (10/25)

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 as the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.

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Statement: Indicator-/ precursor lesion

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Variants of Lobular Neoplasia (11/25)

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).

References:

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LIN with High Risk (12/25)

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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Strategy after Diagnosis of LIN (13/25)

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.

References:

LIN in core- / vacuum-assisted biopsy (LoE 2b)

1. Atkins KA, Cohen MA, Nicholson B, Rao S. Atypical lobular hyperplasia and lobular carcinoma in situ at core breast biopsy: use of careful radiologic-pathologic correlation to recommend excision or observation. Radiology. 2013 Nov;269(2):340-7.

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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) (14/25)

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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Statement: Marker Lesion (LoE 3b)

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Strategy after Diagnosis of FEA (15/25)

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:

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Papilloma (16/25)

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 focused 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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Strategy after Diagnosis of Central Papilloma (17/25)

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. However, this recommendation has been questioned by newer studies. The risk of up-grade is to be considered very low in central papilloma without atypia and not sufficient to justify routine surgical resection.

References:

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Radially Sclerosing Lesion (18/25)

No further information

No references

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL) (19/25)

No further information

No references

Follow-up Imaging for Women Age 50-69 Years with B3-Lesions (20/25)

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:

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Medical Prevention for Women at Increased Risk (including Women with LIN and ADH) (21/25)

Further information:

Risk communication should provide women with information of risk reduction strategies (e.g. follow-up or 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 IBIS-I trial. J Natl Cancer Inst 2007; 99:272-282
3. O'Connor A: Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-354
4. Bozovic-Spasojevic I¹, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F. **Chemoprevention for breast cancer**. Cancer Treat Rev. 2012 Aug;38(5):329-39.

Studies on medical prevention for women at increased risk that included women with LIN and ADH are in **bold**.

Tamoxifen für Frauen > 35 Jahre –Reduktion von DCIS und invasivem Karzinom (LoE 1a A AGO +)

NSABP.P1:

1. 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

IBIS.1

1. Cuzick J: Long-term results of tamoxifen prophylaxis for breast cancer - 96 months follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 2007; 99:272-282.

Royal Marsden
Italian Trial

Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen (LoE 1b A AGO +/-)

MAP.3

1. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winkquist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91.
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IBIS.2

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Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen) (22/25)

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
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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

Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen, Side Effects) (23/25)

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
3. O'Connor A: Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-354

Medical Prevention after Diagnosis of B3 Lesion (Raloxifen) (24/25)

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
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Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors) (25/25)

No further information

References:

Exemestane for breast-cancer prevention in postmenopausal women.

1. Goss PE, Ingle JN, Alés-Martínez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, McTiernan A, Robbins J, Johnson KC, Martin LW, Winqvist E, Sarto GE, Garber JE, Fabian CJ, Pujol P, Maunsell E, Farmer P, Gelmon KA, Tu D, Richardson H; NCIC CTG MAP.3 Study Investigators. N Engl J Med. 2011 Jun 23;364(25):2381-91.
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Chemoprevention for breast cancer.

1. Bozovic-Spasojevic I¹, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Ductal Carcinoma in Situ (DCIS)

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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**

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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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	Oxford / AGO LoE / GR		
➤ Resection margins	1a	A	++
➤ Residual tumor-associated microcalcification	2b	C	++
➤ Age	1a	A	++
➤ Size	1a	A	++
➤ Grading	1a	A	++
➤ Comedo necrosis	1a	A	++
➤ Architecture	2b	C	+
➤ Method of diagnosis	1a	A	++
➤ Focality	1a	A	++
➤ (mod.) Van Nuys Prognostic Index	2b	C	+/-
➤ Palpable DCIS	2b	C	+/-
➤ Palpable + COX-2+, p16+, Ki-67+	2b	C	+/-
➤ Palpable + ER-, HER2+, Ki-67+	2b	C	+/-
➤ HER2/neu (positive vs. negative)	1a	B	+/-
➤ ER/PgR (positive vs. negative)	1a	B	+/-
➤ DCIS-Score	2b	C	+/-
➤ DCIS with microinvasion – treatment in analogy to invasive breast cancer	3b	C	++
➤ Intrinsic subtypes (luminal A, B, HER2+, triple negative)	2b	C	-

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Further
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References

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LEHREN
HEILEN

DCIS Radiotherapy

Oxford / AGO LoE / GR

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: < 2.5 cm, low and intermediate nuclear grade, mammographically detected

* Analysis in ongoing trials

Cochrane Analysis

Radiation after Surgery (all/with Radiation after Breast Conserving Surgery)

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sowie
in der DKG e.V.

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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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Information

References

DCIS Postoperative Systemic Treatment

**Oxford / AGO
LoE / GR**

- | | | | |
|--|-----------|----------|------------|
| ➤ Tamoxifen (only ER+) | 1a | A | + |
| ➤ AI if postmenopausal and
 contraindication against tamoxifen | 5 | D | +/- |
| ➤ Other endocrine options | 5 | D | - |
| ➤ Trastuzumab (only HER2+) | 5 | D | -- |
| ➤ For Prevention of opposite breast see Prevention chapter | | | |

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in der DKG e.V.

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**FORSCHEN
LEHREN
HEILEN**

Cochrane Analysis

Tamoxifen after DCIS (all/with Radiation)

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Guidelines Breast
Version 2015 .1

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.**

**Staley H, McCallum I, Bruce J. Postoperative Tamoxifen for
ductal carcinoma in situ: Cochrane systematic review and
meta-analysis. Breast. 2014 Oct;23(5):546-51. doi:
10.1016/j.breast.2014.06.015. Epub 2014 Jul 9.**

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References

Local Recurrence of DCIS after Tumorectomy w/o Irradiation

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**Oxford / AGO
LOE / GR**

After radiation

- **Simple mastectomy
+ SN B**
- **Second tumorectomy
is followed by recurrences in up to 30 % of patients
(NSABP B17)**

3a	C	+
5	D	+
5	D	+/-

No radiation after first tumorectomy

- **Treatment like primary disease**

3	C	++
----------	----------	-----------

**Prognosis for invasive recurrences seems to be better than
for primary invasive breast cancer. About 50% of
recurrences are invasive.**

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Further
Information

References

**FORSCHEN
LEHREN
HEILEN**

Ductal Carcinoma in Situ (DCIS)

No further information

No references

Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

- **Mammographie**
 - **Vergrößerungsaufnahmen von Mikroverkalkungen**
 - **Steigerung der Detektionsrate von G1/G2 DCIS durch digitale Mammographie (versus konventionell)**
- 1. D'Orsi C: (2010) "Imaging for the Diagnosis and Management of Ductal Carcinoma In Situ" J Natl Cancer Inst Monogr (41) 214 – 217
- 2. Allegra CJ, Alberle DR, Ganschow P et al. National Institutes of Health State-of-the –Science Conference Statement: Diagnosis and Management of Ductal Carcinoma in Situ September 22-24,2009. JNCI 2009;102:161-169
- 3. Allen L, Lago_Toro C, Hughes JH et al. Is there a role for preoperative assessment of patients with DCIS? Ann Surg 2010; 17: 2395-2400
- 4. Farshid G, Sullivan T, Downey P et al. Independent predictors of breast malignancy in screen-detected microcalcifications: biopsy results in 2545 cases. Br J Cancer 2011; 105: 1669 – 1675
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- 6. Lee RJ, Vallow LA, McLaughlin SA, Tzou KS, Hines SL, Peterson JL. Ductal carcinoma in situ of the breast. Int J Surg Oncol. 2012;2012:123549. doi: 10.1155/2012/123549. Epub 2012 Jul 18.
- 7. Nederend J, Duijm LE, Louwman MW, Groenewoud JH, Donkers-van Rossum AB, Voogd AC. Impact of transition from analog screening mammography to digital screening mammography on screening outcome in The Netherlands: a population-based study. Ann Oncol. 2012 Dec;23(12):3098-103. doi: 10.1093/annonc/mds146. Epub 2012 Jun 27.

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➤ **Stereotaktische Stanzbiopsie /
Vakuumbiopsie (VAB)**

1. Houssami, N, D Ambrogetti et al. Accuracy of a Preoperative Model for Predicting Invasive Breast Cancer in Women with Ductal Carcinoma-in-situ on Vacuum-Assisted Core Needle Biopsy. Ann Oncol 2011;18(5):1364-71

➤ **Präparateradiographie**
➤ **Setzen eines Markierungsclips in der Biopsieregion,
wenn die Läsion komplett entfernt wurde**
➤ **MRT zur Festlegung der Ausdehnung**

1. 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.
2. Marcotte-Bloch, C., C. Balu-Maestro, et al. (2009). "MRI for the size assessment of pure ductal carcinoma in situ (DCIS): A prospective study of 33 patients." Eur J Radiol.
3. Neira, P., B. Aguirre, et al. (2009). "[Breast MRI--histologic correlation for ductal carcinoma in situ]." Radiologia 51(4): 396-402.
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- **Klinische Untersuchung**
- **Feinnadelpunktion / duktale Lavage**
- **Interdisziplinäre Tumorboard-Präsentation**

Surgical Treatment for Histologically Proven DCIS I (4/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

➤ **Exzision (drahtmarkiert)**

1. Houssami N, Ambrogetti D, Marinovich L et al. Accuracy of a preoperative model for predicting invasive breast cancer in women with ductal carcinoma in situ on vacuum assisted core needle biopsy. Ann Surg Oncol 2011;18(5):1364-71
2. Saadai P, Moezzi M et al. Preoperative and intraoperative predictors of positive margins after breast-conserving surgery: a retrospective review. Breast Cancer 2011; 18: 221-225
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➤ **Flankierende Drahtmarkierung bei großen Läsionen**

➤ **Präparatradiographie**

➤ **Intraoperative Sonographie (darstellbarer Befund)**

1. Ahmed M, Douek M. Intra-operative ultrasound versus wire-guided localization in the surgical management of non-palpable breast cancers: systematic review and meta-analysis. Breast Cancer Res Treat. 2013; 140(3): 435-446.

➤ **Sofortige Nachresektion bei knappen
Resektionsrändern (Präparateradiographie)**

1. Thill M, Röder K, Diedrich K et al. Intraoperative assessment of surgical margins during breast conserving surgery of ductal carcinoma in situ by use of radiofrequency spectroscopy. *The Breast* 2011(11) 579-580
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➤ **Intraoperative Schnellschnittdiagnostik**

➤ **Interdisziplinäre Tumorboard-Präsentation**

Surgical Treatment for Histologically Proven DCIS II (5/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

➤ Histologisch freie Resektionsränder (pR0)

1. Lagios MD, Page DL, Silverstein MJ. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006;24:3809-11
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➤ Multifokalität: BET falls möglich (inkl. RT)

1. Meijnen P, Bartelink H. Multifocal ductal carcinoma in situ of the breast: A contraindication for breast-conserving treatment? J Clin Oncol 2007;25:5548–5549
2. Rakovitch E, Pignol JP, Hanna W, Narod S, Spayne J, Nofech-Mozes S, Chartier C, Paszat L. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. J Clin Oncol 2007;25:5591–5596

➤ **Nachresektion bei knappem Resektionsrand
(≤ 2 mm im Paraffinschnitt)**

1. Dunne, C., J. P. Burke, et al. (2009). "Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ." J Clin Oncol 27(10): 1615-1620.
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➤ **Mastektomie* (große Läsionen; keine sicheren Ränder im Nachresektat)**

1. Ringberg A, Nordgren H, Thorstensson S, et al. Histopathological risk factors for ipsilateral breast events after breast conserving treatment for ductal carcinoma in situ of the breast--results from the Swedish randomised trial. Eur J Cancer 2007;43:291-8
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3. Solin LJ. Is excision alone adequate treatment for low-risk ductal carcinoma-in-situ of the breast? J Clin Oncol 2006;24:1017-1019
4. Vargas C, Kestin L, Go N, et al. Factors associated with local recurrence and cause-specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy. Int J Radiat Oncol Biol Phys 2005;63:1514-21
5. Carlson, G. W., A. Page, et al. (2007). "Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy." J Am Coll Surg 204(5): 1074-1078; discussion 1078-1080.
6. Rudloff U, E Brogi et al. (2010): "The Influence of Margin Width and Volume of Disease Near Margin on Benefit of Radiation Therapy for Women With DCIS Treated With Breast-Conserving Therapy" Ann Surg (251) 583 – 591

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8. Houssami N, Ambrogetti D, Marinovich L et al. Accuracy of a preoperative model for predicting invasive breast cancer in women with ductal carcinoma in situ on vacuum assisted core needle biopsy. Ann Surg Oncol 2011;18(5):1364-71

➤ **SNE***

- **Mastektomie**
- **DCIS beim Mann**

1. Chern J, Liao L, Baraldi R, Tinney E, Hendershott K, Germaine P. Case report: ductal carcinoma in situ in the male breast. Case Rep Radiol. 2012;2012:532527. doi: 10.1155/2012/532527. Epub 2012 Sep 26.

➤ **BET: ≥ 5 cm oder $> 2,5$ cm + high grade/Komedonekrosen**

2. Meijnen P, Oldenburg HS, Loo CE, Nieweg OE, Peterse JL, Rutgers EJ. Risk of invasion and axillary lymph node metastasis in ductal carcinoma in situ diagnosed by core-needle biopsy. Br J Surg 2007;94:952-6
3. Miyake T, Shimazu K, Ohashi H, et al. Indication for sentinel lymph node biopsy for breast cancer when core biopsy shows ductal carcinoma in situ. The American Journal of Surgery 2011; 202: 59-65 :394095. doi: 10.5402/2012/394095. Epub 2012 May 14.

➤ **Axilladisektion**

DCIS – Prognostic Factors for the Incidence of Local- /Locoregional Recurrence (6/11)

No further information

References:

- **Resektionsränder**
 - **Residualer tumorassoziierter Mikrokalk**
 - **Alter**
 - **Größe**
 - **Grading**
 - **Komedonekrose**
 - **Architektur**
1. Ringberg A, Nordgren H, Thorstensson S, et al. Histopathological risk factors for ipsilateral breast events after breast conserving treatment for ductal carcinoma in situ of the breast--results from the Swedish randomised trial. Eur J Cancer 2007;43:291-8
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 6. Kerlikowske K, AM Molinaro et al. Biomarker Expression and Risk of Subsequent Tumors After Initial Ductal Carcinoma In Situ Diagnosis. J Natl Cancer Inst 2010; 102: 627 – 637

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8. Cuzick J, I Sestak et al. Effect of Tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK / ANZ DCIS trial. *Lancet Oncol* 2011; 12: 21- 29
9. Lari S, Kuerer HM. Review: Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. *Journal of Cancer* 2011; 2: 232-261
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12. King TA, Sakr RA, Muhsen S, et al. Is there a Low-Grade Precursor Pathway in Breast Cancer? *Ann Surg Oncol* 2011;(epub ahead)
13. Chan P, Lim S. Predictors of Invasive Breast Cancer in Ductal Carcinoma In Situ initially diagnosed by Core Biopsy. *Asian J Surg* 2010; 33: 76-82
14. Liao N, Zhang GC, Liu YH, et al. HER2-positive status is an independent predictor for coexisting invasion of ductal carcinoma in situ of the breast presenting extensive DCIS component. *Pathology Res Practice* 2011; 207: 1-7
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16. Brennan ME, Turner RM, Ciatto S, et al. Ductal Carcinoma in Situ at Core-Needle Biopsy: Meta-Analysis of Underestimation and Predictors of Invasive Breast Cancer. *Radiology* 2011; 260: 119-128
17. Wang S, Shamliyan T, Virnig BA, et al. Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. *Breast Cancer Res Treat* 2011; 127: 1-14
18. Holmes P, Lloyd J, Chervoneva I, et al. Prognostic Markers and Long-Term Outcomes in Ductal Carcinoma In Situ of the Breast Treated With Excision Alone. *Cancer* 2011; 117: 3650-7

➤ **Diagnostische Methode**

1. Han JS, Molberg KH, Sarode V. Predictors of Invasion and Axillary Lymph Node Metastasis in Patients with a Core Biopsy Diagnosis of Ductal carcinoma In Situ: An Analysis of 255 Cases. *The Breast Journal* 2011; 17: 223-229

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➤ **Fokalität**

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2. Rakovitch E, Pignol JP, Hanna W, Narod S, Spayne J, Nofech-Mozes S, Chartier C, Paszat L. Significance of multifocality in ductal carcinoma in situ: outcomes of women treated with breast-conserving therapy. *J Clin Oncol* 2007;25:5591–5596

➤ **(mod.) Van Nuys Prognose Index**

1. Lagios MD, Page DL, Silverstein MJ. Prospective study of wide excision alone for ductal carcinoma in situ of the breast. *J Clin Oncol* 2006;24:3809-11
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5. Altintas S, Toussaint J, Durbecq V, et al. Fine Tuning of the Van Nuys Prognostic Index (VNPI) 2003 by Integrating the Genomic Grade Index (GGI): New Tools for Ductal Carcinoma In Situ (DCIS). The Breast Journal 2011; 17: 343-351
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7. Silverstein MJ, Lagios MD. Choosing Treatment for Patients With Ductal Carcinoma In Situ: Fine Tuning the University of Southern California/Van Nuys Prognostic Index. J natl Cancer Inst Monogr 2010; 41: 193-196

➤ **Palpables DCIS**

➤ **Palpabel + COX-2+p16+Ki-67+**

➤ **Palpabel + ER-, HER2, +Ki-67+**

➤ **HER2-Überexpression**

➤ **ER/PgR (positiv vs. negativ)**

➤ **DCIS-Score**

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➤ **DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom**

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DCIS Radiotherapy (7/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

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Radiotherapie nach:

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Sonderformen der Radiotherapie:

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Oncology of Arizona, Translational Research Center, Scottsdale, AZ; South Florida Radiation Oncology, LLC, Boynton Beach, FL; Virginia Hospital Center, Arlington, VA; Drexel University College of Medicine, Philadelphia, PA; Arizona Breast Cancer Specialists, Scottsdale, AZ; The Christ Hospital Cancer Center, Cincinnati, OH; 21st Century Oncology, Translational Research Consortium (TRC), Fort Myers, FL; Texas Oncology, Denton, TX; Northwest Community Hospital Cancer Services, Arlington Heights, IL; Kerri Perry, MD, Denton, TX; Schiffler Cancer Center, Wheeling, WV; Helen F. Graham Cancer Center - Christiana Care Health System, Newark, DE.

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➤ **Boost-RT des Tumorbettes**

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Bei Patientinnen unter 45-50 Jahren

Cochrane Analysis – Radiation after Surgery (8/11)

No further information

No references

DCIS Postoperative Systemic Treatment (9/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

➤ **Tamoxifen (nur ER+, nur BET)**

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- **AI (wenn postmenopausal und Kontraindikationen gegen Tamoxifen)**
- **Andere endokrine Optionen -**
- Trastuzumab (nur HER2+)**

1. Cobleigh MA, Anderson SJ, Julian TB, Siziopikou KP, Arthur DW, Rabinovitch R, Zheng P, Mamounas EP, Wolmark N. 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). SABCS 2012; OT1-2-01
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Cochrane Analysis – Tamoxifen after DCIS (10/11)

No further information

No references

Local Recurrence of DCIS after Tumorectomy w/o Irradiation (11/11)

Further information and references:

Abstimmung:

Lokalrezidiv des DCIS nach Tumorektomie nach Radiatio:

Einfache Mastektomie

++ 4/19;
+ 15/19

Einfache Mastektomie + SNB:

++ 3/22
+ 14/22
+/- 3/22
- 2/22
-- 0/22

Lokalrezidiv des DCIS nach Tumorektomie mit Radiotherapie

Therapieindikation wie bei primärer Erkrankung:

++ 10/21
+ 7/21
+/- 1/21
- 1/21
-- 2/21

Nach Radiatio

➤ **Einfache Mastektomie**

+ SN B

1. Silverstein MJ, MD Lagios et al (1998): “Outcome After Invasive Local Recurrence in Patients With Ductal Carcinoma In Situ of the Breast” J Clin Oncol 16:1367-1373
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Keine Radiotherapie

Therapieindikation wie bei primär Erkrankung

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Surgery Oncological Aspects

Breast Cancer Surgery

Oncological Aspects

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AGO: ++

Surgery is only one sub-step out of multiple steps in breast cancer treatment. Thus, both a diagnostic and an oncological expertise are indispensable and a definite requirement.

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Further
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 significant 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

Perioperative Staging

**Oxford / AGO
LoE / GR**

- **History and physical examination**

5 D ++

Only recommended in high metastatic potential and / or with 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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Further
Information

References

**FORSCHEN
LEHREN
HEILEN**

Breast Conservation: Surgical Technical Aspects

Oxford / AGO LoE / GR

➤ Non-palpable lesion

- Wire guided localisation
- Radionuclide guided localisation
- Specimen radiography or ultrasound

2b B ++

2b B +/-

2b B ++

➤ Tumor-free margins required

(also in unfavorable biology „no cells on ink“ are enough)

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 +/-

Breast Conservation Surgery (BCS)

**Oxford / AGO
LoE / GR**

- **Multicentricity**
- **Positive microscopic margins
after repeated excision**
- **Inflammatory breast cancer**

2b B +/-

2b B - -

2b B - -

Surgery after neoadjuvant chemotherapy go to chapter „neoadjuvant chemotherapy“

Axillary Lymph Node Dissection I

Oxford / AGO LoE / GR

Axillary lymph node dissection (≥ 10 LN)

- To improve survival
- For staging
- For local control

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

Axillary lymph node dissection:

- DCIS
- If SLNB is possible
- SN + (cT1/2 cN*0; < 3 SN +, BCS + tangential radiation field, no subsequent axillary radiation, adequate systemic therapy)
- SN + (mic)
- SN (i+)
- SN + mastectomy (no radiotherapy of the chestwall)
- SN+ mastectomy (radiotherapy of the chestwall)
 - Only if T1, T2 and 1-2 pos. SLN

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

Axillary lymph node dissection indicated, but not feasible

- Radiation according to AMAROS-trial

1b ^a	B	+/-
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* Study participation recommended

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				2b	B	+
SLNB post NACT*				2a	B	+/-
Surgical Procedure according to lymph node status						
cN-status (prior therapy)	pN-status (prior therapy)	cN-status (after therapy)	Surgical procedure			
cN0	pN0(sn)	-	nihil	1a	A	+
cN0	pN+(sn) acc. ACOSOG Z11** criteria	ycN0	ALND	3	B	+/-
cN0	pN+(sn) <u>not</u> acc. to ACOSOG Z11** criteria	ycN0	ALND	2b	B	+
cN+	cN+ (CNB/FNA)	ycN0	SNB ALND	2a 2b	B B	+/- +
		ycN+ (CNB/FNA)	ALND	2b	B	++

*radiocolloid and blue dye,
study participation recommended

* *T1/T2, BCS, 1-2 SLN pos., breast radiation

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Further
Information

References

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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	2a	B	+

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Sentinel Lymph Node Excision (SNE): Indications II

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➤ During pregnancy and / or breast feeding (no blue dye)	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

Sentinel Lymph Node Excision (SNE): Marking

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➤ ^{99m}Tc Kolloid	1a	A	++
➤ Blue dye	1a	B	+/-
➤ Methylen blue	4	D	-
➤ Indocyanin green (ICG)*	2b	B	+/-
➤ SPIO*	2b	B	+/-

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SPIO: Superparamagnetic Iron Oxide

*** Study participation recommended**

Procedure after Neoadjuvant Therapy

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	Oxford / AGO LoE / GR		
➤ Marking of tumor in a timely manner	5	D	++
➤ Surgery	2b	C	++
➤ Microscopically clear margins	5	D	++
➤ Tumor resection in the new margins	3b	C	+

Surgery after neoadjuvant chemotherapy go to chapter „Neoadjuvant chemotherapy“

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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	3b	C	+

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Further
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References

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Breast Cancer Surgery Oncologic Aspects (2 and 3/15)

Further information and references: Thill M., Rezai M..

Update Januar 2015

Screened data bases: Pubmed 1998 - 2015, ASCO 2014, SABCS 2014, ESMO 2014, EBCC 2014

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.
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Cochrane library:

- <http://onlinelibrary.wiley.com/cochranelibrary/search>

Pretherapeutic assessment (4/15)

No further information

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Pre-operative staging (5/15)

No further information

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Statement: history and physical examination

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Statement: high metastatic potential / symptoms

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Evidence of surgical procedure (6/15)

No further information

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Breast conservation, surgical technical aspects (7/15)

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Breast Conservation Surgery (8/15)

No further information

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Axillary Lymph Node Dissection I (9/15)

No further information

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Surgical Treatment of Axillary Lymph Nodes Pre and Post Nact (10/15)

No further information

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Sentinel Lymph Node Excision: Indications I (11/15)

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Sentinel Lymph Node Excision: Indications II (12/15)

No further information

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Statement: previous major breast surgery

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Statement: Others

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Sentinel Lymph node excision: Marking (13/15)

No further information

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Procedure after neoadjuvant treatment (14/15)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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**Audretsch / Blohmer / Brunnert / Dall /
Fersis / Hanf / Kümmel / Lux / Nitz / Rezai /
Rody / Scharl / Thomssen**

- **Version 2015:**
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Use of plastic surgical techniques at the time of tumor excision to enable safe resection margins and to preserve aesthetic breast contour.

Oncoplastic surgery reduces the number of reexcisions, increases the number of BCTs and leads to high patient satisfaction.

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Oncoplastic Breast Conserving Surgery

Oxford / AGO
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➤ Reduction mammaplasty	2a	B	+
➤ Mastopexy techniques	3a	B	+
➤ Oncoplastic flap techniques	2a	B	+
➤ Partial mastectomy with tissue transfer	3b	B	+

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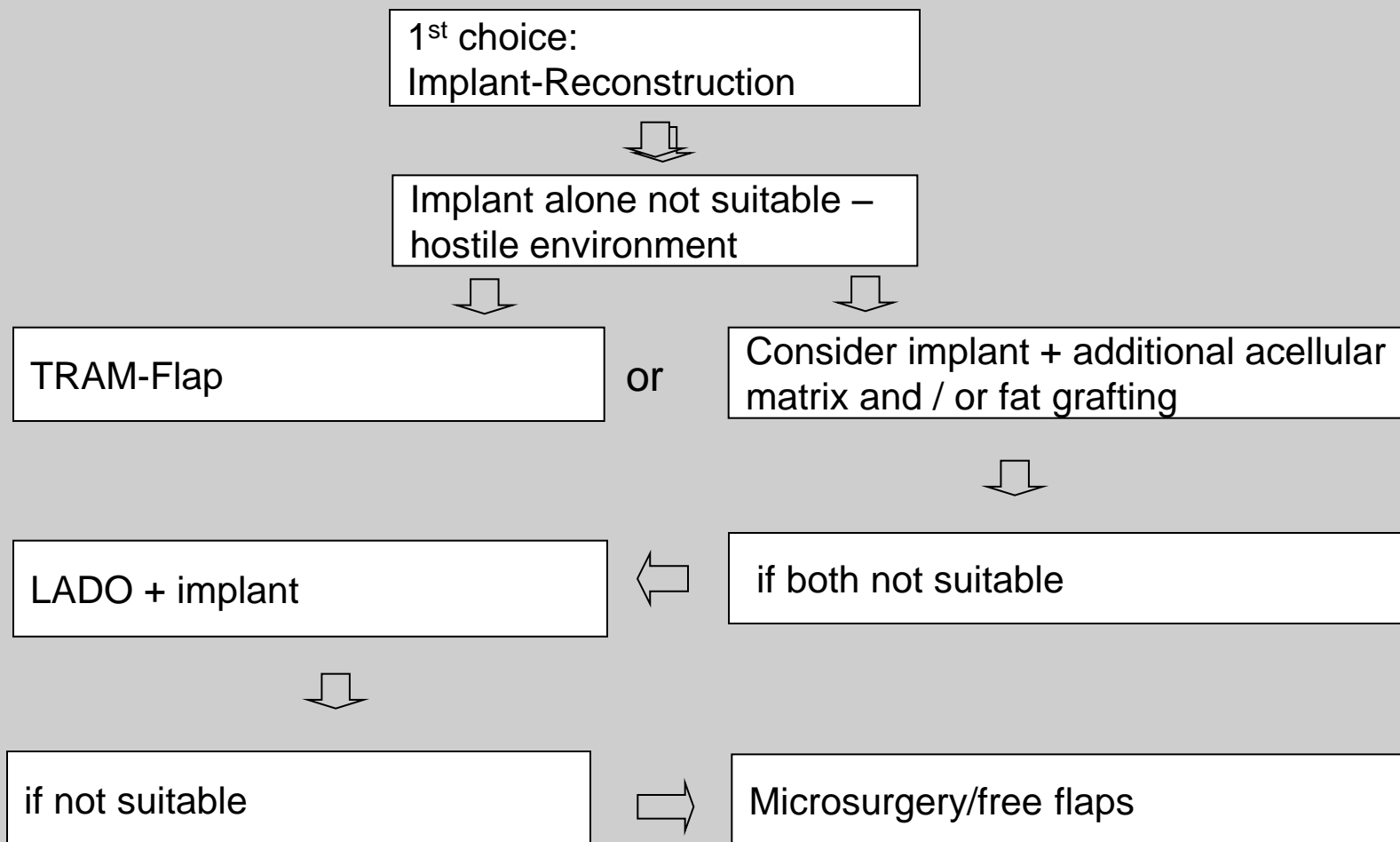
References

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Postmastectomy Reconstruction

Oxford / AGO LoE / GR

- | | | | |
|---|-----------|----------|----------|
| ➤ Use of silicone filled breast implants | 2a | B | + |
| ➤ Autologous tissue reconstruction | 2a | B | + |
| ➤ Pedicled tissue reconstruction | 2a | B | + |
| ➤ Free tissue reconstruction | 2a | B | + |
| ➤ Autologous tissue combined with implants | 3a | C | + |

Attention: BMI >30, smoking status, Diabetes, RT, age

Timing of 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 ++

- Mandatory: SSM / NSM
- Avoidance of a postmastectomy syndrome

➤ „Delayed-immediate“ BR

3b B +/-

Timing of Postmastectomy Implant Reconstruction

Oxford / AGO LoE / GR

➤ Implant reconstruction (IR)

- IR without radiotherapy (RT)
- IR following MX and RT
- IR prior to RT / following PBRT
(higher complication rate)
- IR following Mx for local relapse after
BCT
- Periop. antibiotic therapy (at least 48 h)

2a	B	+
2a	B	++
2b	B	+/-
2a	B	+
2a	B	+/-
3b	C	+

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Soft Tissue Replacement Techniques

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- **Autologous tissue (e.g. LDF*)**
- **Acellular dermal matrix (ADM)**
- **Synthetic mesh**

3b	C	+[#]
2b	B	+[#]
2b	B	+[#]

* LDF = Latissimus dorsi flap

Participation in register studies recommended

Lipotransfer

Oxford / AGO
LoE / GR

➤ **Lipotransfer after MX and breast reconstruction**

2a B +

➤ **Lipotransfer after breast-conserving therapy**

4 D +/-

➤ **Autologous adipose derived stem cells (ASCs)-enriched fat grafts**

5 D -

Postmastectomy Pedicled Reconstruction

**Oxford / AGO
LoE / GR**

Reconstruction (BR) with autologous tissue

➤ **TRAM, latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)**

3b C +

➤ **Delayed TRAM in risk patients**

3a B +

➤ **Ipsilateral pedicled TRAM**

3b A +

➤ **Radiotherapy:**

➤ **BR following RT**

2 a B +

➤ **BR prior to RT**

2a B +/-

(more fibrosis, more wound healing problems, more liponecrosis)

Free Tissue Transfer

**Oxford / AGO
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Free tissue transfer

- **Free TRAM-flap**
- **DIEP-flap**
- **SIEA-flap**
- **SGAP- / IGAP-flap**
- **Free gracilis flap (TMG)**

3a	B	+/-
3a	B	+
3a	C	+/-
4	C	+/-
4	C	+/-

Advantage:

- Free TRAM, DIEP are potentially muscle-sparing procedures. The DIEP has a lower rate of abdominal hernias.

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

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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

LDF* + implant

- IR following RT
- IR prior to RT

2b	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

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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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

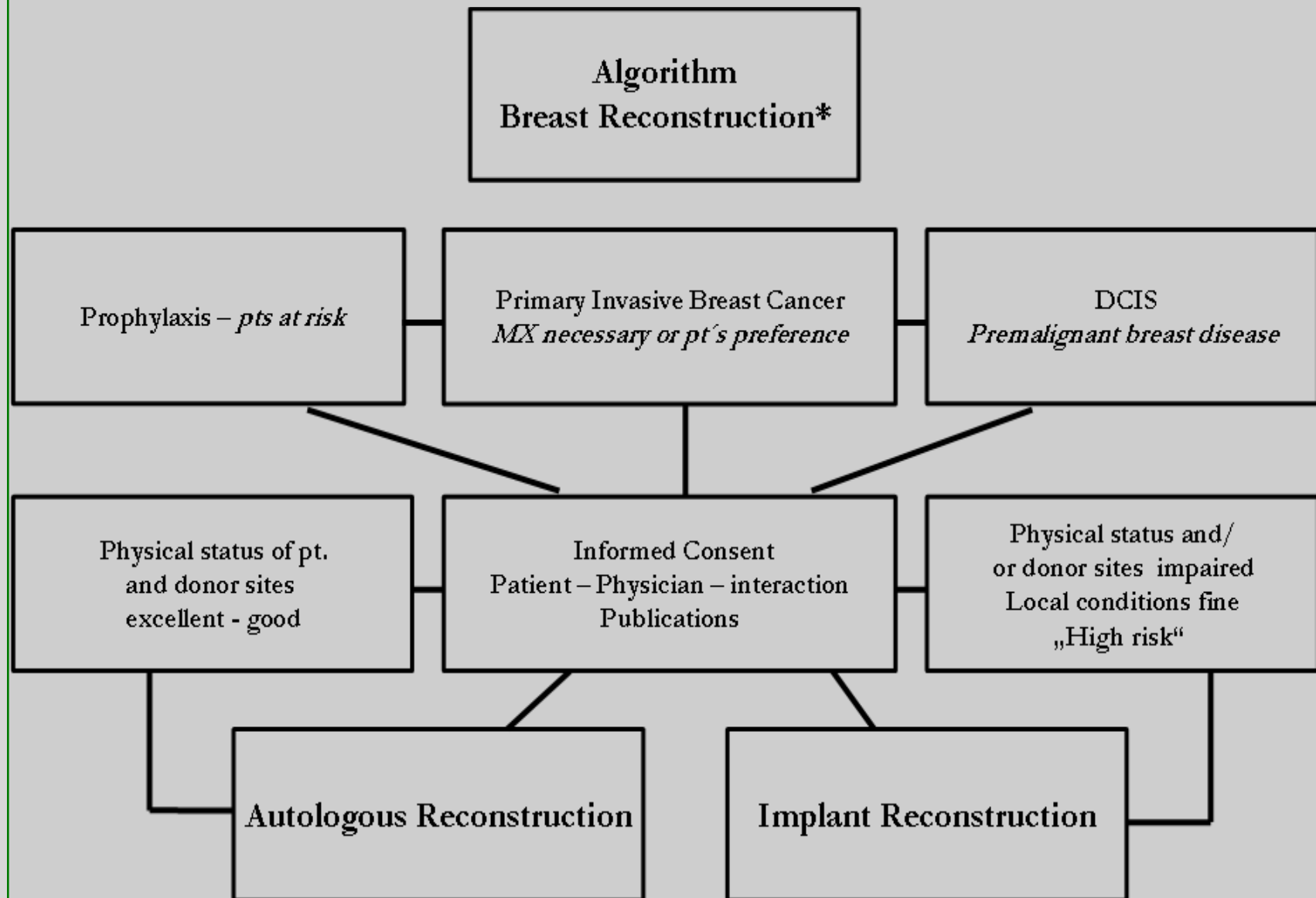
Types of Risk Reducing Mastectomy

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	+/-

Algorithm of Breast Reconstruction



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

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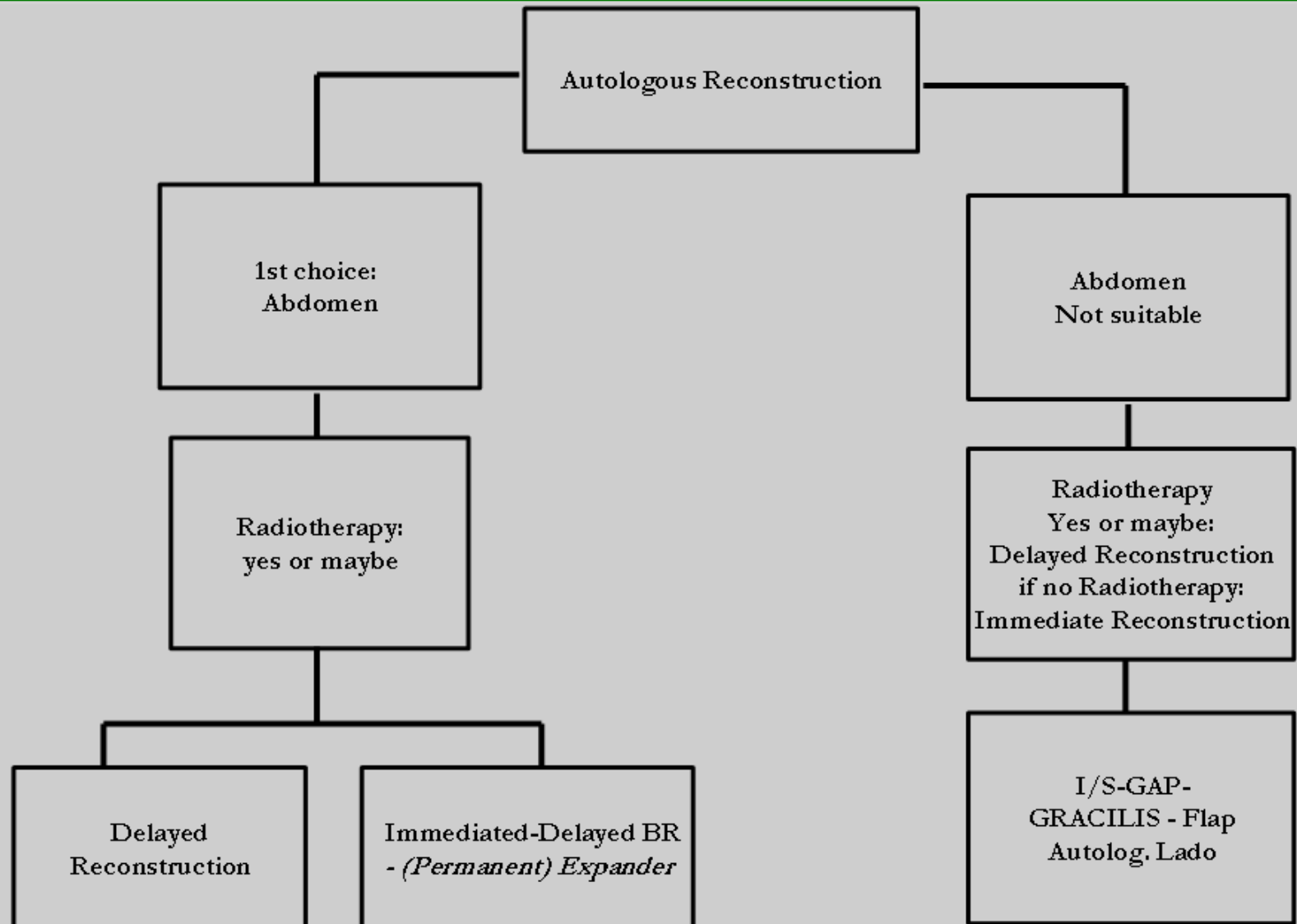
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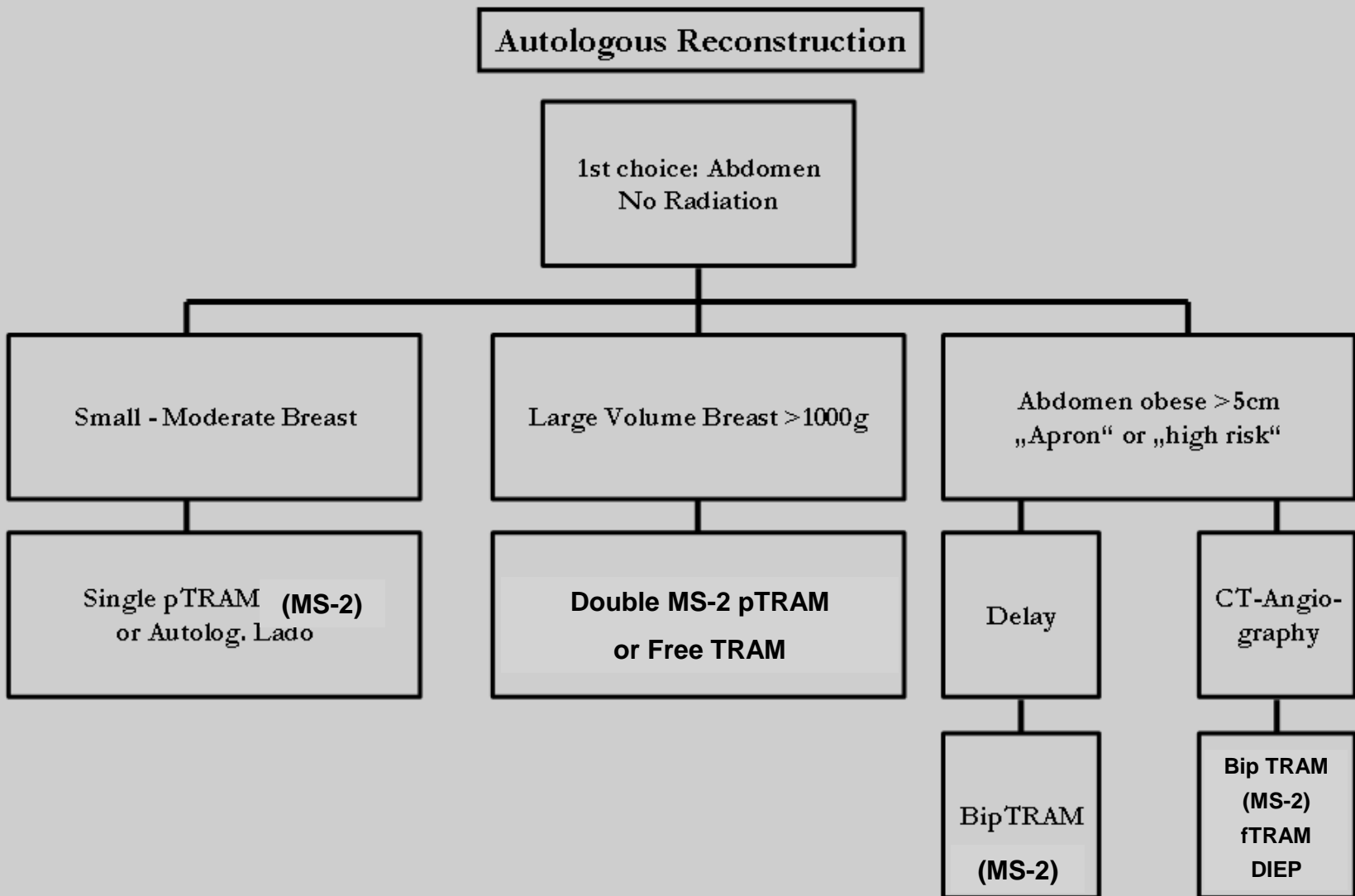
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Algorithm of Autologous Breast Reconstruction (2)

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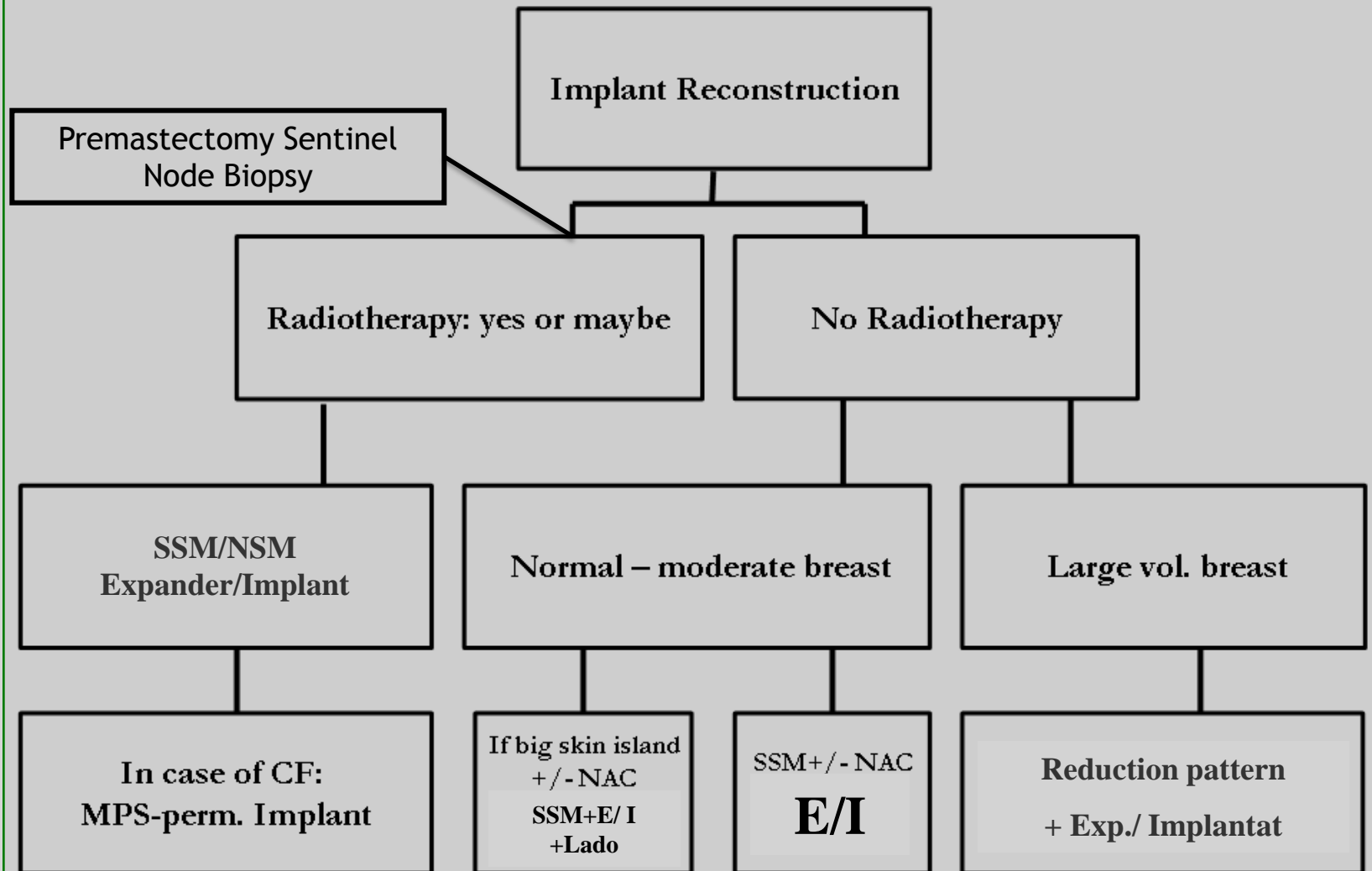


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Algorithm of Implant Breast Reconstruction



E = expander ; I = implant; CF = Capsula fibrosis; MPS = micropolyurethan surface

Oncoplastic and Reconstructive Surgery (2/21)

Further information and references:

Literature research

Pubmed 2003 – 01/2015

Cochrane data base (z.B. Cochrane Breast Cancer Specialised Register)

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>

Definition of oncoplastic surgery (3/21)

Further information:

AGO Voting for giving a new definition 45/0

References:

Definition modified after: Oncoplastic techniques in breast conserving surgery

Benjamin Anderson, MD; Kristine Calhoun, MD [http://www.uptodate.com/contents/oncoplastic-techniques-in-breast-conserving-](http://www.uptodate.com/contents/oncoplastic-techniques-in-breast-conserving-surgery?source=machineLearning&search=oncoplastic+surgery&selectedTitle=1%7E1§ionRank=1&anchor=H14027079#H14027079)

[surgery?source=machineLearning&search=oncoplastic+surgery&selectedTitle=1%7E1§ionRank=1&anchor=H14027079#H14027079](http://www.uptodate.com/contents/oncoplastic-techniques-in-breast-conserving-surgery?source=machineLearning&search=oncoplastic+surgery&selectedTitle=1%7E1§ionRank=1&anchor=H14027079#H14027079)

Oncoplastic breast conserving surgery (4/21)

Further information:

AGO Voting for this new slide and content 45/0

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Algorithm of Breast Reconstruction (5/21)

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No voting this year

No references

Postmastectomy Reconstruction (6/21)

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Voting for this new slide and content 45/0

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Timing of Reconstruction (7/21)

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No voting this year

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Timing of Postmastectomy Implant Reconstruction (8/21)

Further information:

AGO voting for implant reconstruction before radiation:

23 voting for +

2 voting for +/-

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Soft tissue replacement techniques (9/21)

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Lipotransfer (10/21)

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Ago voting for changing the wording from “lipofilling” to “Lipotransfer”: 45/0

Voting for new wording statement 1: 45/0

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Postmastectomy (pedicled) Reconstruction (11/21)

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Voting for whole content with one consent

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Free Tissue Transfer (12/21)

Further information:

Voting:

For Free TRAM-flap 11 +; 12 +/-

DIEP-flap + with one consent

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Pedicled vs. Free Tissue Transfer (13/21)

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No voting this year

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Flap-Implant Combination (14/21)

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No voting this year

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Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction (15/21)

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No voting this year

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Bilateral Risk Reducing Mastectomy in healthy women (RRBM) (16/21)

Further information:

No voting this year

Please see chapter breast Cancer Risk and Prevention

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Types of Risk Reducing Mastectomy (17/21)

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Algorithm of Breast Reconstruction (18/21) and
Algorithm of Autologous Breast Reconstruction (1) (19/21) and
Algorithm of Autologous Breast Reconstruction (2) (20/21) and
Algorithm of Implant Breast Reconstruction (4) (21/21)

Further information:

No voting this year

No references

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References

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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

Further
Information

References

Adjuvant Endocrine Therapy

Assessment of Menopausal Status

Oxford / AGO
LoE / GR

Assessment of menopausal status

- Menstruation history +
- FSH, E2 ++

Adjuvant Endocrine Therapy

Oxford / AGO
LoE / GR

Standard therapy in endocrine responsive tumors:

- **Endocrine therapy** 1a A ++
- **Chemotherapy followed by endocrine therapy** 1a A ++
(dependent on individual risk and tumor biology)

Adjuvant Endocrine Therapy

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➤ **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 ++

- **Standard treatment duration 5 years**
- **Treatment up to 10 years may be considered based on the individual risk of relapse (e.g., N+ status at presentation)**
- **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 postmenopausal patients at high risk and lobular cancers**
- **So far no evidence for AI > 5 yrs**

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Premenopausal Patients

Adjuvant Endocrine Therapy

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- **Tamoxifen* 5-10 yrs.**
- **GnRHa alone**
(only if relevant contraindications for Tam)

1a	A	++
1a	B	+

**In patients with ovarian function (within 8 mo.)
after adjuvant chemotherapy (exploratory retrospective
analysis suggests higher benefit in younger age)**:**

- **#OFS (ovarian function suppression) 5 yrs. + TAM 5 yrs.**
- **#OFS 5 yrs. + AI 5 yrs.**

1b	B	+/-
1b	B	+/-

OFS (ovarian function suppression)

- * **Treat as long as tolerable and premenopausal**
- * **Switch to AI optional when patient turned postmenopausal**
- # **increased side effects may impair compliance. High compliance to TAM ist more effective, than addition of GNRH or treatment with GNRH+AI with impaired compliance.**
- ** **Duration of treatment may be prolonged to up to 10 yrs using TAM**

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Premenopausal Patients

Adjuvant Endocrine Therapy

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- | | | | |
|--|-----------|----------|-----------|
| ➤ 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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Postmenopausal Patients Adjuvant Endocrine Therapy

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➤ **AI for 5 yrs.**

- Preference in lobular inv. cancers

1a A +

➤ **Sequential therapy for 5 -10 yrs.**

- Tam followed by AI (2-5 yrs.)*

1a A

- AI (2-5 yrs.)* followed by Tam

1b C

Preference in N+

++

➤ **Tamoxifen 20 mg/d for 5-10 yrs.**

1a A ++

***Duration of AI ≤ 5 yrs.**

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

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LoE / GR**

Ovarian Function Protection

CT + GnRHa (Interaction with CT unclear)

1b B +/-

(GnRHa application > 2 weeks prior to chemotherapy)

Impairment of CT – effect cannot be excluded!

Fertility preservation counselling

4 C +

Fertility preservation with

assisted reproduction therapy

4 C +

Testing Ovarian Reserve

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**Assessment of ovarian reserve in
infertile patients
(>6-12 mths without conception)***

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5 C +

Tests for fertility assessment

➤ **Anti-Müllerian Factor**

3b B +/-

➤ **Antral follicle count**

3b B +/-

* Tests are suggested for women > 35yrs and infertility for 6-12 months; the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated and infertility treatment may be considered.

Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer

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	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

Ovarian Function Preservation – Comparison of Randomized Trials

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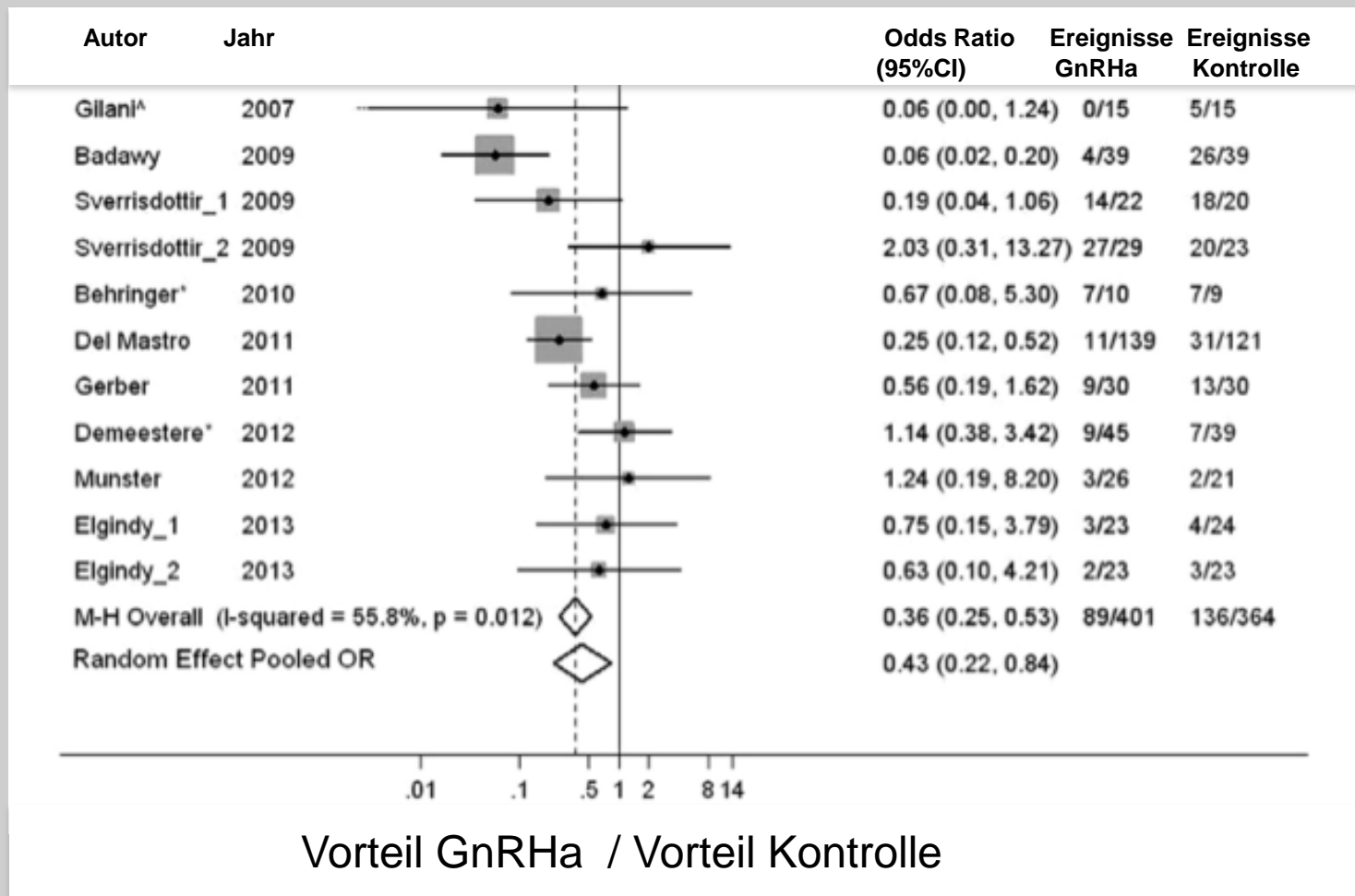
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	ZORO	PROMISE	Munster et al. - US	POEMS
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years
Treatment	goserelin	triptorelin	triptorelin	goserelin
Start of treatment	>2 weeks prior to cht	>1 week 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	Ovarian failure at 2 yrs 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%	
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predicitive factor
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	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%
Median time to restoration of menses (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	n.d.
Cyclophosph. dose	4600 vs. 4700mg	4080 vs. 4008 mg	n.r.	n.a.

Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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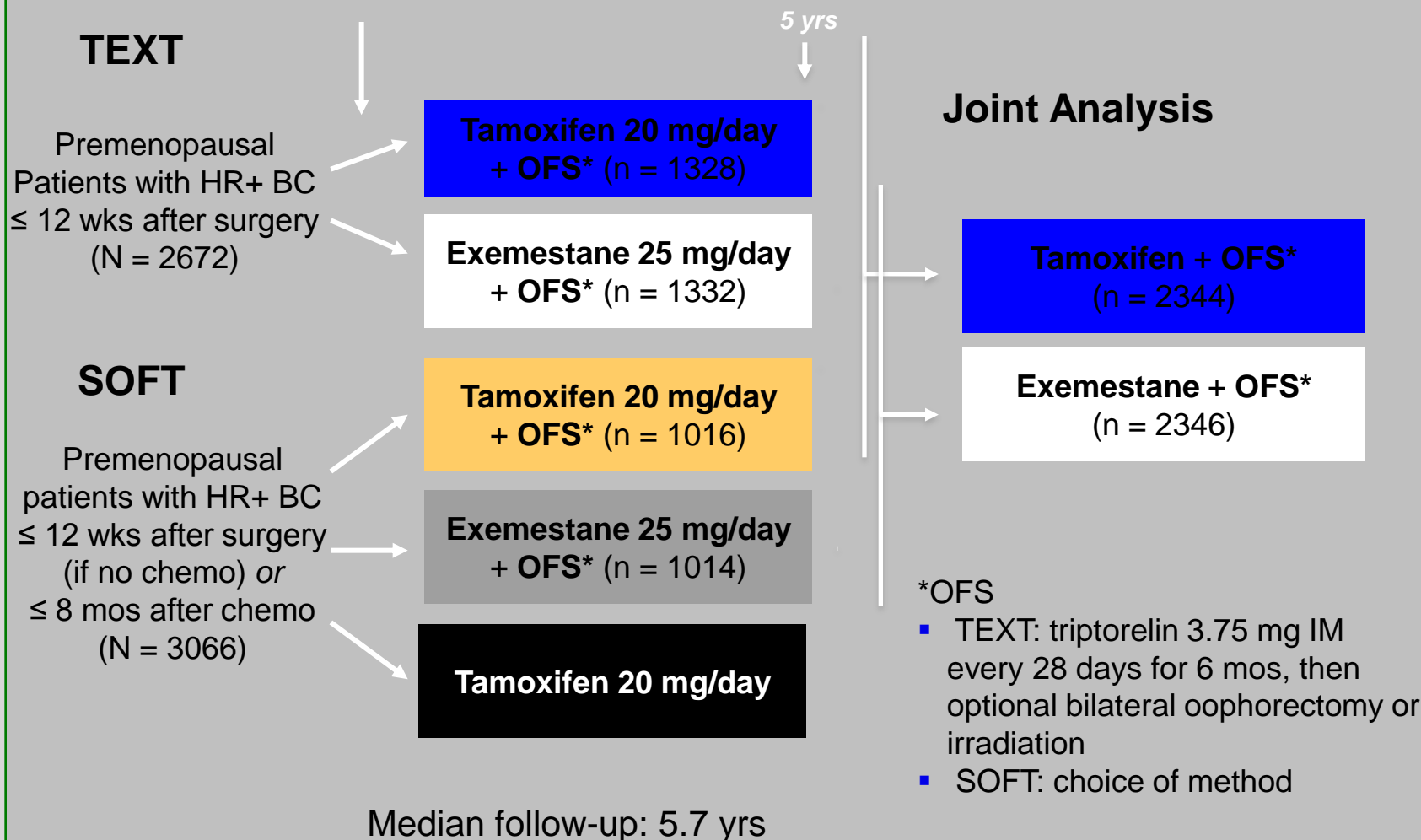
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Overview over Published Trials: Upfront and Extended Therapy

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+

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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References

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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Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserved (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268–273

Test	Details
FSH (follicle stimulating hormone) plus estradiol	<ul style="list-style-type: none"> • Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation
Anti Müllerian Hormone (AMH)	<ul style="list-style-type: none"> • No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation
Antral follicle count (AFC)	<ul style="list-style-type: none"> • Number of visible follicles (2–10 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.

10 yrs versus 5 yrs Breast Cancer Mortality in ER+

Rate ratio per period in aTTom and ATLAS

5 yrs. vs. 10 yrs Tamoxifen

	10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)	10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)	10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) p = 0.07	0.75 (0.63-0.90) p = 0.002	0.75 (0.65-0.86) p = 0.00004
All years	0.88 (0.74-1.03) p = 0.1	0.83 (0.73-0.86) p = 0.004	0.85 (0.77-0.94) P= 0.001

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nach Grey et al ASCO 2013
J Clin Oncol 31, 2013 (suppl. Abstr 5)

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/20)

No further information

No references

Assessment of Steroid Hormone Receptor Status (3/20)

No further information

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Adjuvant Endocrine Therapy (5/20)

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Adjuvant Endocrine Therapy (6/20)

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General Principles of Adjuvant Endocrine Therapy AGO ++ (7/20)

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Voting: 18/7

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Premenopausal Patients - Adjuvant endocrine therapy (8/20)

Further information and references:

Tamoxifen* 5-10 yrs.

1a A ++ Voting: 100% acceptance

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. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011 Aug 27;378(9793):771-84. doi: 10.1016/S0140-6736(11)60993-8. Epub 2011 Jul 28
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4. Tormey DC, Gray R, Falkson HC: Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. J Natl Cancer Inst 88 (24): 1828-33, 1996.

GnRHa alone

1a B + Voting: 100% acceptance

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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4. Goel S et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004562.
5. Cuzick J et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007; 369:1711-23.

in patients with ovarian function (within 8 mo.) after adjuvant chemotherapy (Exploratory retrospective analysis suggests higher benefit in younger age)

OFS (ovarian function suppression) 5 yrs. + TAM 5 yrs.	1b	B	+/-	Voting: 100% acceptance
OFS 5 yrs. + AI 5 yrs.	1b	B	+/-	Voting: 100% acceptance

1. Pagani O, Gelber S, Colleoni M et al. Impact of SERM adherence on treatment effect: International Breast Cancer Study Group Trials 13-93 and 14-93. Breast Cancer Res Treat. 2013 Nov;142(2):455-9. doi: 10.1007/s10549-013-2757-x. Epub 2013 Nov 7.
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3. Goel S et al: LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004562.
4. Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, Bonnefoi HR, Climent MA, Prada GA, Burstein HJ, Martino S, Davidson NE, Geyer CE Jr, Walley BA, Coleman R, Kerbrat P, Buchholz S, Ingle JN, Winer EP, Rabaglio-Poretti M, Maibach R, Ruepp B, Giobbie-Hurder A, Price KN, Colleoni M, Viale G, Coates AS, Goldhirsch A, Gelber RD; the SOFT Investigators and the International Breast Cancer Study Group. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med. 2014 Dec 11. [Epub ahead of print]
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Coates AS, Gelber RD, Goldhirsch A, Francis PA; TEXT and SOFT Investigators; International Breast Cancer Study Group. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014 Jul 10;371(2):107-18. doi: 10.1056/NEJMoa1404037. Epub 2014 Jun 1.

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Premenopausal Patients – Adjuvant Endocrine Therapy (9/20)

Further information and references:

AI alone 1c A - - Voting: 100% acceptance

1. Smith IE et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006 Jun 1;24(16):2444-7
2. Ortmann O, et al: Adjuvant endocrine therapy for perimenopausal women with early breast cancer. Breast. 2009 Feb;18(1):2-7
3. Dieudonné AS, Vandenberghe J, Geerts I, Billen J, Paridaens R, Wildiers H, Neven P. Undetectable antimüllerian hormone levels and recovery of chemotherapy-induced ovarian failure in women with breast cancer on an oral aromatase inhibitor. Menopause. 2011 Jul;18(7):821-4.

AI after GnRHa (induced amenorrhea) 5 D - - Voting: 100% acceptance

1. Smith IE et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006 Jun 1;24(16):2444-7
4. Dieudonné AS, Vandenberghe J, Geerts I, Billen J, Paridaens R, Wildiers H, Neven P. Undetectable antimüllerian hormone levels and recovery of chemotherapy-induced ovarian failure in women with breast cancer on an oral aromatase inhibitor. Menopause. 2011 Jul;18(7):821-4.
5. Goss PE et al: Outcomes of women who were premenopausal at diagnosis of early stage breast cancer. Cancer Res 69(Suppl.1);2009:487s(#13)

Upfront AI in patients with chemotherapy-induced amenorrhea (CIA, TIA) 4 C - - Voting: 100% acceptance

1. Smith IE et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006 Jun 1;24(16):2444-7

**EAT in perimenopausal pts. with validated
postmenopausal status after 5 yrs. of Tam**

2b B

+

Voting: 100% acceptance

1. Smith IE et al: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol. 2006 Jun 1;24(16):2444-7
2. Goss PE et al: Outcomes of women who were premenopausal at diagnosis of early stage breast cancer. Cancer Res 69(Suppl.1);2009:487s(#13)

Postmenopausal patients – adjuvant endocrine therapy (10/20)

Further information and references:

AI for 5 yrs.	1a	A	+	Voting: 100% acceptance
Preference in lobular inv. Cancers	2b	B	+	Voting: 100% acceptance

1. Baum M et al.. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002 Jun 22;359:2131-9. Erratum in: Lancet 2002;360:1520.
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3. BIG 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747-57.
4. Coates AS et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine responsive early breast cancer: update of study BIG 1-98 J Clin Oncol, pub ahead January 2007
5. Cella D et al. Five years quality of life follow up of adjuvant endocrine therapy for postmenopausal women in the ATAC trial. Proc ASCO 2005, Abstract 577.
6. Duffy S. Gynecological adverse events including hysterectomy with anastrozole tamoxifen: Data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. J Clin Oncol 2005;23(Suppl.):58S, Abs 723.

Sequential therapy for 5 -10 yrs.			++	
Tam followed by AI (2-5 yrs.)*	1a	A		
AI (2-5 yrs.)* followed by Tam	1b	C		Voting: 100% acceptance

1. Goss PE et al. a randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer N Engl J Med 2003; 349: 1793-1802
2. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97:1262-71.
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4. Mamounas E et al. Benefit from exemestane as extended adjuvant therapy after 5 years of tamoxifen intent to treat analysis of the NSABP-B33. Breast Cancer Res and Treat 2006; 100 (suppl1):abstract 49.
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Tamoxifen 20 mg/d for 5-10 yrs. 1a A ++ Voting: 100% acceptance

1. Davies C, Hongchao P, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet, published online 2012
2. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of randomised trials. Lancet 2005;365:1687-717.
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4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet, 378:771-84, 2011

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT) **(11/20)**

Further information and references:

Ovarian Function Protection

CT + GnRH α (Wechselwirkung mit CT unklar) 1b B +/-
(GnRH α application > 2 weeks prior to chemotherapy) Voting: 100% acceptance

1. Gerber B: Controversies in preservation of ovary function and fertility in patients with breast cancer. Breast Cancer Res Treat. 2008 Mar;108(1):1-7.
2. Tham YL: The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am J Clin Oncol. 2007; 30:126-32
3. Recchia F, Saggio G, Amiconi G et al. (2006) Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. Cancer 106: 514-523
4. Fox K, Scialla J, Moore H: Preventing chemotherapy-related amenorrhea using leuprolide during adjuvant chemotherapy for early-stage breast cancer. Proc Am Soc Clin Oncol 22, 13. 2003.
5. Del Mastro L, Catzeddu T, Boni L et al. (2006) Prevention of chemotherapy-induced menopause by temporary ovarian suppression with goserelin in young, early breast cancer patients. Ann Oncol 17: 74-78
6. 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
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chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. *Cancer Treat Rev.* 2014 Jun;40(5):675-83. doi: 10.1016/j.ctrv.2013.12.001. Epub 2013 Dec 8.

Fertility preservation counselling*	4	C	+	Voting: 100% acceptance
Fertility preservation with assisted reproduction therapy	4	C	+	Voting: 100% acceptance

1. Lawrenz B, Jauckus J, Kupka MS et al. Fertility preservation in >1,000 patients: patient's characteristics, spectrum, efficacy and risks of applied preservation techniques. *Arch Gynecol Obstet.* 2010 Dec 1. [Epub ahead of print].
2. Shalom-Paz E, Almog B, Shehata F et al. Fertility preservation for breast-cancer patients using IVM followed by oocyte or embryo vitrification. *Reprod Biomed Online.* 2010 Oct;21(4):566-71. Epub 2010 May 13.
3. Besse D, Bellavia M, de Ziegler D, Wunder D. Fertility and cancer: psychological support in young women who contemplate emergency assisted reproductive technologies (ART) prior to chemo- and/or radiation-therapy. *Swiss Med Wkly.* 2010 Jul 16;140:w13075. doi: 10.4414/smw.2010.13075.
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5. Munster PN, Moore AP, Ismail-Khan R, Cox CE, Lacey M, Gross-King M, Xu P, Carter WB, Minton SE. Randomized Trial Using Gonadotropin-Releasing Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer. *J Clin Oncol.* 2012 Jan 9. [Epub ahead of print]
6. Loibl S, Gerber B. Gonadotropin-releasing hormone analogue for premenopausal women with breast cancer. *JAMA.* 2011 Oct 26;306(16):1760; author reply 1760-1.

Testing ovarian reserve (12/20)

No further information

References:

1. Su HI, Sammel MD, Green J, Velders L, Stankiewicz C, Matro J, Freeman EW, Gracia CR, DeMichele A. Antimüllerian hormone and inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. *Cancer*. 2010 Feb 1;116(3):592-9.
2. Partridge AH, Ruddy KJ, Gelber S, Schapira L, Abusief M, Meyer M, Ginsburg E. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril*. 2010 Jul;94(2):638-44.
3. Anders C, Marcom PK, Peterson B, Gu L, Unruhe S, Welch R, Lyons P, Behera M, Copland S, Kimmick G, Shaw H, Snyder S, Antenos M, Woodruff T, Blackwell K. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. *Cancer Invest*. 2008 Apr-May;26(3):286-95.
4. Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. *J Clin Endocrinol Metab*. 2011 May; 96(5):1336-43.
5. ACOG Committee Opinion No. 618: Ovarian Reserve Testing. *Obstetrics & Gynecology* 2015 ;125 : 268–273
6. Su HI, Chung K, Sammel MD, Gracia CR, DeMichele A. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. *Fertil Steril*. 2011 Apr;95(5):1857-9.

Contraceptive Options for Premenopausal Women after Diagnosis of Breast Cancer (13/20)

No further information

References:

1. Backman T, Use of the levonorgestrel-releasing intrauterine system and breast cancer. Obstet Gynecol. 2005 Oct;106(4):813-7.
2. Strom BL, Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer. Contraception. 2004 May;69(5):353-60.
3. Moormann PG, Havrilesky LJ, Giersch JM et al. 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.

Ovarian Function Preservation (14/20)

No further information

No references

Metaanalysis of GnRH for Prevention of Premature Ovarian Failure (15/20)

No further information

No references

TEXT/SOFT Joint Analysis (16/20)

No further information

No references

Aromataseinhibitors in Adjuvant Therapy (17/20)

No further information

No references

Aromataseinhibitors in Adjuvant Therapy – Overview over Published Trials (18/20)

No further information

No references

Assessment of Ovarian Reserve (19/20)

No further information

No references

10 Yrs versus 5 yrs Breast Cancer Mortality in ER+ (20/20)

No further information

No references

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 2003–2014:**
Harbeck / Jackisch / Janni / Loibl / von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Solomeyer / Stickeler / Thomssen / Untch
- **Version 2015:**
Schütz / Lux

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LEHREN
HEILEN

Subtype-specific General Systemic Strategies

AGO

**If chemotherapy is indicated due to tumor biology,
consider systemic treatment before surgery (neoadjuvant)**

++

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, carboplatinum-containing regimen
 - Dose dense & escalated in case of high tumor burden

++

++

+

+

TNBC

- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated

++

+

Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview

**Oxford / AGO
LoE / GR**

➤ **Anthracycline / taxane based
chemotherapy**

1a A ++

➤ **If anthracyclines cannot be given**

➤ **Docetaxel plus cyclophosphamide**

1b B +

➤ **Paclitaxel mono weekly**

1b B +/-

➤ **CMF**

1a A +/-

➤ **Dose-dense in case of high tumor
burden**

1a A ++

Recommended Regimens for Adjuvant Chemotherapy

Oxford / AGO
LoE / GR

Anthracycline / taxane based regimen

➤ EC → P _w	E ₉₀ C q3w x 4 → P ₈₀ qw1 x 12	1b ^a	B	++
➤ DAC	D ₇₅ A ₅₀ C q3w x 6	1b	A	++
➤ AC → P _w	A ₆₀ Cq3w x 4 → P ₈₀ qw1 x 12	1b	A	++
➤ AC → D	A ₆₀ C q3w x 4 → D ₁₀₀ qw3 x 4	1b	A	++
➤ EC → D	E ₉₀ C q3w x 4 → D ₁₀₀ qw3 x 4	1b ^a	B	++

Anthracycline-free regimen

➤ DC	D ₇₅ C ₆₀₀ x4	1b	B	+
➤ Pac mono	P ₈₀ q1w x 12	1b	B	+/-
➤ CMF	C ₆₀₀ M ₄₀ F ₆₀₀ q3w x 6	1a	A	+/-

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Dose-dense and/ or Dose-escalated Adjuvant Chemotherapy in Case of High Tumor Burden

Oxford / AGO
LoE / GR

Dose-dense regimen

- AC q3w / Pac q1w x 12
- *EC q3w Pac q1w x 12
- EC q3w / Pac q2w
- EC q2w / Pac q1w
- ACPac / AC-Pac q2w

1b	A	++
1b	B	++
1b ^a	A	+
1b	B	+
1b	A	+

Dose-dense and dose-escalated regimen (N ≥ 4+)

- E-Pac-C q2w

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

* Extrapolated from doxorubicin trials

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Adjuvant Chemotherapy other Drugs

**Oxford / AGO
LoE / GR**

- | | | | |
|--|-----------------------|----------|------------|
| ➤ Capecitabine containing regimen in TNBC | 1a | B | +/- |
| ➤ Platinum containing regimen in TNBC | 5 | D | +/- |
| ➤ 5- Fluorouracile added to EC/AC | 1b^a | A | - - |

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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 -

1b A +/-

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References

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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Adjuvant Treatment with Trastuzumab: Schedules

**Oxford / AGO
LoE / GR**

Simultaneously

- **With paclitaxel / docetaxel after AC / EC**
- **With P q1w 12 x without A in pT < 3 cm, pN0**
- **With docetaxel and carboplatin**

- **With anthracyclines**
- **With taxanes dose-dense**

1b A ++

2b^a B +/-

1b A +

2b B +/-

2b B + *

Radiotherapy concurrent with Trastuzumab

2b B +

*** Study participation recommended**

Adjuvant Therapy with Other Targeted Agents

Oxford / AGO
LoE / GR

- **Lapatinib**
 - (delayed adjuvant treatment)

5 D -

1b B -

- **Lapatinib + Trastuzumab**

1b^a B -

- **Pertuzumab**

5 D -

- **Bevacizumab**

1b^a B --

Adjuvant Cytotoxic and Targeted Therapy (2/12)

No further information

No references

Subtype-specific general systemic strategies (3/12)

No further information:

References:

1. Schmidt M. Chemotherapy in early breast cancer: when, how and which one? Breast Care (Basel). 2014 Jul;9(3):154-60.
2. 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.

Adjuvant Chemotherapy without concurrent trastuzumab: overview (4/12)

Further information and references:

Statement: Anthracycline/ taxane based chemotherapy (1a A ++)

Vote result of the AGO recommendation: 100%

1. Budd GT, Barlow WE, Moore HC, Hobday TJ, Stewart JA, Isaacs C, Salim M, Cho JK, Rinn KJ, Albain KS, Chew HK, Burton GV, Moore TD, Srkalovic G, McGregor BA, Flaherty LE, Livingston RB, Lew DL, Gralow JR, Hortobagyi GN. SWOG S0221: A Phase III Trial Comparing Chemotherapy Schedules in High-Risk Early-Stage Breast Cancer. *J Clin Oncol*. 2015 Jan 1;33(1):58-64.
2. Nitz U, Gluz O, Huober J, Kreipe HH, Kates RE, Hartmann A, Erber R, Scholz M, Lisboa B, Mohrmann S, Möbus V, Augustin D, Hoffmann G, Weiss E, Böhmer S, Kreienberg R, Du Bois A, Sattler D, Thomssen C, Kiechle M, Jänicke F, Wallwiener D, Harbeck N, Kuhn W. Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. *Ann Oncol*. 2014 Aug;25(8):1551-7.

Statement:

If anthracyclines cannot be given - Docetaxel plus cyclophosphamide (1b B +)

Vote result of the AGO recommendation: 100%

1. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, Pippin JE, Bordelon JH, Kirby RL, Sandbach J, Hyman WJ, Richards DA, Mennel RG, Boehm KA, Meyer WG, Asmar L, Mackey D, Riedel S, Muss H, Savin MA. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *Clin Oncol*. 2009 Mar 10;27(8):1177-83.

Statement:

If anthracyclines cannot be given - Paclitaxel mono weekly (1b B +/-)

Vote result of the AGO recommendation: 100%

1. Amoroso V, Pedersini R, Sharratt P, Vassalli L, Ferrari L, Sigala S, Simoncini E, Berruti A. Should adjuvant weekly Paclitaxel be considered less efficacious than anthracyclines plus cyclophosphamide for lower-risk patients with early-stage breast cancer? J Clin Oncol. 2015 Jan 20;33(3):290.
2. Shulman LN, Berry DA, Cirrincione CT, Becker HP, Perez EA, O'Regan R, Martino S, Shapiro CL, Schneider CJ, Kimmick G, Burstein HJ, Norton L, Muss H, Hudis CA, Winer EP. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 Aug 1;32(22):2311-7.
3. 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

Statement:

If anthracyclines cannot be given - CMF (1a A +/-)

Vote result of the AGO recommendation: 100%

1. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, Pacilio C, Rossi E, De Laurentiis M, D'Aiuto M, Botti G, Forestieri V, Lauria R, De Placido S, Tinessa V, Daniele B, Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, de Matteis A. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. Ann Oncol. 2014 Dec 8. pii: mdu564. [Epub ahead of print]
2. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. N Engl J Med. 1995 Apr 6;332(14):901-6

Statement: Dose-dense in case of high tumor burden (1a A ++)

Vote result of the AGO recommendation: 100%

1. Moylan EJ, Connell LC, O'Reilly S. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014 Feb 20;32(6):605-6.

2. Lemos Duarte I, da Silveira Nogueira Lima JP, Passos Lima CS, Deeke Sasse A. Dose-dense chemotherapy versus conventional chemotherapy for early breast cancer: a systematic review with meta-analysis. *Breast*. 2012 Jun;21(3):343-9.
3. Moebus V, 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. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol*. 2010 Jun 10;28(17):2874-80.

Recommended Regimens for Adjuvant Chemotherapy (5/12)

Further information and references:

Statement: Anthracycline/ taxane based regimen

EC → Pw E90C q3w x 4 → P80 qw1 x 12 (1b B ++)

Vote result of the AGO recommendation: 100%

1. Budd GT, Barlow WE, Moore HCF, et al: S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer. J Clin Oncol 31:51s, 2013 (suppl; abstr CRA1008)
2. Sparano JA, Zhao F, Martino S, Ligibel J, Saphner T, Wolff AC, Sledge GW, Perez EA, Wood WC, Davidson NE. Ten year update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer. SABCs, S3-03, 2014

Statement: Anthracycline/ taxane based regimen

DAC D75A50C q3w x 6 (1b A ++)

Vote result of the AGO recommendation: 100%

1. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Brufsky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N. 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. J Clin Oncol. 2013 Sep 10;31(26):3197-204. doi: 10.1200/JCO.2012.48.1275. Epub 2013 Aug 12.

Statement: Anthracycline/ taxane based regimen

AC → Pw A60Cq3w x 4 → P80qw1 x 12 (1b A ++)

Vote result of the AGO recommendation: 100%

1. Eleftherios P. Mamounas, John Bryant, Barry Lembersky, Louis Fehrenbacher, Scot M. Sedlacek, Bernard Fisher, D. Lawrence Wickerham, Greg Yothers, Atilla Soran, and Norman Wolmark. Paclitaxel After Doxorubicin Plus Cyclophosphamide As Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results From NSABP B-28 J Clin Oncol 2005. 23:3686-3696.

Statement: Anthracycline/ taxane based regimen

AC → D A60C q3w x 4 → D100 qw3 x 4 (1b A ++)

EC → D E90C q3w x 4 → D100 qw3 x 4 (1ba B ++)

Statement: Anthracycline-free regimen

DC D75 C600 x4 (1b B +)

Vote result of the AGO recommendation: 100%

1. Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, Pippin JE, Bordelon JH, Kirby RL, Sandbach J, Hyman WJ, Richards DA, Mennel RG, Boehm KA, Meyer WG, Asmar L, Mackey D, Riedel S, Muss H, Savin MA. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. Clin Oncol. 2009 Mar 10;27(8):1177-83.

Statement: Anthracycline-free regimen

Pac mono 80 mg q1w x 4-6 (1b B +/-)

Vote result of the AGO recommendation: 100%

1. Shulman LN, Berry DA, Cirincione CT, Becker HP, Perez EA, O'Regan R, Martino S, Shapiro CL, Schneider CJ, Kimmick G, Burstein HJ, Norton L, Muss H, Hudis CA, Winer EP. Comparison of doxorubicin and cyclophosphamide versus single-agent paclitaxel as adjuvant therapy for breast cancer in women with 0 to 3 positive axillary nodes: CALGB 40101 (Alliance). J Clin Oncol. 2014 Aug 1;32(22):2311-7.

Statement: Anthracycline-free regimen

CMF 600/40/600 mg q3w x 6 (1a A +/-)

Vote result of the AGO recommendation: 100%

1. Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, Pacilio C, Rossi E, De Laurentiis M, D'Aiuto M, Botti G, Forestieri V, Lauria R, De Placido S, Tinessa V, Daniele B, Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, de Matteis A. Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. *Ann Oncol.* 2014 Dec 8. pii: mdu564. [Epub ahead of print]

Dose-dense and/ or dose-escalated adjuvant chemotherapy in case of high tumor burden (6/12)

Further information and references:

Statement: Dose-dense regimen

AC q3w / Pac q1w x 12 (1b A++)

**EC q3w Pac q1w x 12 (1b B++)*

Vote result of the AGO recommendation: 100%

1. Burnell M, Levine MN, Chapman JA, Bramwell V, Gelmon K, Walley B, et al. Cyclophosphamide, epirubicin, and fluorouracil versus dose-dense epirubicin and cyclophosphamide followed by paclitaxel versus doxorubicin and cyclophosphamide followed by paclitaxel in node-positive or high-risk node-negative breast cancer. J Clin Oncol 2010;28:77e82.

Statement: Dose-dense regimen

EC q3w / Pac q2w (1ba A+)

EC q2w / Pac q1w (1b B+)

Vote result of the AGO recommendation: 100%

1. Venturini M, Del Mastro L, Aitini E, Baldini E, Caroti C, Contu A, et al. Dosedense adjuvant chemotherapy in early breast cancer patients: results from a randomized trial. J Natl Cancer Inst 2005;97:1724e33
2. Jones RL, Walsh G, Ashley S, Chua S, Agarwal R, O'Brien M, et al. A randomized pilot phase II study of doxorubicin and cyclophosphamide (AC) or epirubicin and cyclophosphamide (EC) given 2 weekly with pegfilgrastim (accelerated) vs 3 weekly (standard) for women with early breast cancer. Br J Cancer 2009;100:305e10.

Statement: Dose-dense regimen

ACPac / AC-Pac q2w (1b A+)

Vote result of the AGO recommendation: 100%

1. Citron ML, Berry DA, Cirincione C, Hudis C, Winer EP, Gradishar WJ, et al. 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. *J Clin Oncol* 2003;21:1431e9.

Statement: Dose-dense and dose-escalated regimen ($N \geq 4+$)

E-Pac-C q2w (1b A ++)

Vote result of the AGO recommendation: 100%

1. Moebus V, 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. Intense dose-dense sequential chemotherapy with epirubicin, paclitaxel, and cyclophosphamide compared with conventionally scheduled chemotherapy in high-risk primary breast cancer: mature results of an AGO phase III study. *J Clin Oncol*. 2010 Jun 10;28(17):2874-80.

Negative Trial

1. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan PP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Brufsky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N. 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. *J Clin Oncol*. 2013 Sep 10;31(26):3197-204.

Adjuvant Chemotherapy Other Drugs (7/12)

Further information and references:

Statement: Capecitabine containing regimen in TNBC (1a B +/-)

Vote result of the AGO recommendation: 100%

1. Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R, Jukkola-Vuorinen A, Tanner M, Kokko R, Ahlgren J, Auvinen P, Pajja O, Helle L, Villman K, Nyandoto P, Nilsson G, Pajunen M, Asola R, Poikonen P, Leinonen M, Kataja V, Bono P, Lindman H. Adjuvant capecitabine, docetaxel, cyclophosphamide, and epirubicin for early breast cancer: final analysis of the randomized FinXX trial. J Clin Oncol. 2012 Jan 1;30(1):11-8. doi: 10.1200/JCO.2011.35.4639. Epub 2011 Nov 21.
2. Jiang Y, Yin W, Zhou L, Yan L, Zhou Q, Du Y, Shen Z, Shao Z, Lu J. First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis. PLoS ONE 2012 7(3): e32474.

Statement: Platinum containing regimen in TNBC (5 D +/-)

Vote result of the AGO recommendation: 100%

No References available.

Statement: 5- Fluorouracile added to EC/AC (1ba A - -)

Vote result of the AGO recommendation: 100%

1. Cignetti F, Bruzzi P, De Placido S, De Laurentiis M, Boni C, Aitini E, Durando A, Turletti 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. 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 . San Antonio Breast Cancer Symposium 2013. S5-06.

Adjuvant treatment with trastuzumab I (8/12)

Further information and references:

Statements: Node-positive and node-negative disease

Vote result of the AGO recommendation: 100%

1. 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, Gatrex V, Ward C, Strähle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005 Oct 20;353(16):1659-72.
2. 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. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007 Jan 6;369(9555):29-36.
3. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013 Sep 21;382(9897):1021-8.
4. Jackisch C, Kim SB, Semiglazov V, Melichar B, Pivot X, Hillenbach C, Stroyakovskiy D, Lum BL, Elliott R, Weber HA, Ismael G. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. *Ann Oncol*. 2014 Nov 17. pii: mdu524. [Epub ahead of print]

Statements: >10 mm/> 5-10 mm/ <= 5mm

1. 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 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. J Clin Oncol. 2009 Dec 1;27(34):5700-6. Epub 2009 Nov 2.

Adjuvant treatment with Trastuzumab II (9/12)

Further information and references:

Statement: Start of treatment

Vote result of the AGO recommendation: 100%

1. 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. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005 Oct 20;353(16):1673-84.
2. 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, Gatrex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005 Oct 20;353(16):1659-72.
3. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, Utriainen T, Kokko R, Hemminki A, Tarkkanen M, Turpeenniemi-Hujanen T, Jyrkkio S, Flander M, Helle L, Ingalsuo S, Johansson K, Jääskeläinen AS, Pajunen M, Rauhala M, Kaleva-Kerola J, Salminen T, Leinonen M, Elomaa I, Isola J; FinHer Study Investigators. *N Engl J Med.* 2006 Feb 23;354(8):809-20.
4. 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. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet.* 2007 Jan 6;369(9555):29-36.
5. E. A. Perez, E. H. Romond, V. J. Suman, J. Jeong, N. E. Davidson, C. E. Geyer, S. Martino, E. P. Mamounas, P. A. Kauffman, N. Wolmark, NCCTG/NSABP. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. *Journal of*

Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 512

6. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, Utriainen T, Turpeenniemi-Hujanen T, Jyrkkiö S, Möykkynen K, Helle L, Ingalsuo S, Pajunen M, Huusko M, Salminen T, Auvinen P, Leinonen H, Leinonen M, Isola J, Kellokumpu-Lehtinen PL. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol. 2009 Dec 1;27(34):5685-92. Epub 2009 Nov 2.
7. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. PLoS One. 2011;6(6):e21030. Epub 2011 Jun 9.
8. 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. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 29:4491-4497. 2011
9. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83. doi: 10.1056/NEJMoa0910383.
10. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8. doi: 10.1016/S0140-6736(13)61094-6. Epub 2013 Jul 18.

Statement: Duration

Duration Trastuzumab 1 year

Vote result of the AGO recommendation: 100%

Duration Trastuzumab 2 year

Vote result of the AGO recommendation: 100%

Duration Trastuzumab 0.5 years

Vote result of the AGO recommendation: 1 +/ 23 +/- 6 -/ 1 --

1. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013 Sep 21;382(9897):1021-8.
2. 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.
3. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. 2013 Jul;14(8):741-8.

Adjuvant trastuzumab – Cardiac monitoring for CHF (10/12)

Further information and references:

Statement: Cardiac Monitoring

Vote result of the AGO recommendation: 100%

1. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. J Clin Oncol. 2004 Jan 15;22(2):322-9.
2. Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, Perren T, Passalacqua R, Bighin C, Klijn JG, Ageev FT, Hitre E, Groetz J, Iwata H, Knap M, Gnant M, Muehlbauer S, Spence A, Gelber RD, Piccart-Gebhart MJ. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol. 2007 Sep 1;25(25):3859-65. Epub 2007 Jul 23.
3. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, Martino S, Gralow JR, Dakhil SR, Ingle JN, Winer EP, Gelmon KA, Gersh BJ, Jaffe AS, Rodeheffer RJ. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol. 2008 Mar 10;26(8):1231-8. Epub 2008 Feb 4.
4. Mackey JR, Clemons M, Côté MA, Delgado D, Dent S, Paterson A, Provencher L, Sawyer MB, Verma S. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. Curr Oncol. 2008 Feb;15(1):24-35.
- 5.

Adjuvant treatment with trastuzumab: Schedules (11/12)

Further information and references:

Statement: with paclitaxel/docetaxel after AC/EC

Vote result of the AGO recommendation: 100%

1. 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. Sequential Versus Concurrent Trastuzumab in Adjuvant Chemotherapy for Breast Cancer. J Clin Oncol 29:4491-4497. 2011
2. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, Jackisch C, Cameron D, Weber HA, Heinzmann D, Dal Lago L, McFadden E, Dowsett M, Untch M, Gianni L, Bell R, Köhne CH, Vindevoghel A, Andersson M, Brunt AM, Otero-Reyes D, Song S, Smith I, Leyland-Jones B, Baselga J; Herceptin Adjuvant (HERA) Trial Study Team. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8.

Statement: P q1w12 without A in pT < 3 cm pN0

Vote result of the AGO recommendation: 100%

1. Tolaney 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. A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). SABCS 2013. S1-04
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Statement: with docetaxel and carboplatin

Vote result of the AGO recommendation: 100%

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2. Harold J. Burstein, Martine J. Piccart-Gebhart, Edith A. Perez, Gabriel N. Hortobagyi, Norman Wolmark, Kathy S. Albain, Larry Norton, Eric P. Winer, Clifford A. Hudis. Choosing the Best Trastuzumab-Based Adjuvant Chemotherapy Regimen: Should We Abandon Anthracyclines? *Journal of Clinical Oncology*, Vol 30, No 18 (June 20), 2012: pp 2179-2182

Statement: with anthracyclines

Vote result of the AGO recommendation: 100%

See references slide 8.

Statement: with taxanes dose-dense

Vote result of the AGO recommendation: 100%

See references slide 8.

Statement: radiotherapy concurrent with trastuzumab

Vote result of the AGO recommendation: 100%

1. M. Y. Halyard, T. M. Pisansky, L. J. Solin, L. B. Marks, L. J. Pierce, A. Dueck, E. A. Perez. 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. Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 523

Adjuvant Therapy with Other Agents (12/12)

Further information and references:

Statement: with Lapatinib

Vote result of the AGO recommendation: 100%

1. Moreno-Aspitia A1, Dueck AC, Ghanem-Cañete I, Patel T, Dakhil S, Johnson D, Franco S, Kahanic S, Colon-Otero G, Tenner KS, Rodeheffer R, McCullough AE, Jenkins RB, Palmieri FM, Northfelt D, Perez EA. RC0639: phase II study of paclitaxel, trastuzumab, and lapatinib as adjuvant therapy for early stage HER2-positive breast cancer. *Breast Cancer Res Treat.* 2013 Apr;138(2):427-35.
2. Goss PE1, Smith IE, O'Shaughnessy J, Ejlertsen B, Kaufmann M, Boyle F, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Chavarri-Guerra Y, Aktan G, Rappold E, Williams LS, Finkelstein DM; TEACH investigators. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2013 Jan;14(1):88-96.
3. Piccart-Gebhart M, Holmes AP, Baselga J, de Azambuja E, Dueck A, Viale G, Zujewski JA, Goldhirsch A, Santillana S, Pritchard K, Wolff A, Jackisch C, Lang I, Untch M, Smith I, Boyle F, Xu B, Gomez H, Gelber RD, Perez EA. First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC). ASCO, 2014

Statement: with Lapatinib + Trastuzumab

Vote result of the AGO recommendation: 100%

1. Piccart-Gebhart M, Holmes AP, Baselga J, de Azambuja E, Dueck A, Viale G, Zujewski JA, Goldhirsch A, Santillana S, Pritchard K, Wolff A, Jackisch C, Lang I, Untch M, Smith I, Boyle F, Xu B, Gomez H, Gelber RD, Perez EA. First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC). ASCO, 2014

Statement: Pertuzumab

Vote result of the AGO recommendation: 100%

Trials are ongoing. No final results available.

Statement: Bevacizumab

Vote result of the AGO recommendation: 100%

1. 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. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. *Lancet Oncol.* 2013 Sep;14(10):933-42.
2. D.Slamon, S.Swain, M.Buyse, M.Martin, C.Geyer, Y-H.Im, T.Pienkowski, S-B.Kim, N.Robert, G.Steger, J.Crown, S.Verma, W.Eiermann, J.Costantino, SA.Im, E.Mamounas, L.Schwartzberg, A.Paterson, J.Mackey, L.Provencher, M.Press, M.Thirlwell, V.Bee-Munteanu, V.Henschel, A.Crepelle-Flechais, N.Wolmark. BETH: A Randomized Phase III Study Evaluating Adjuvant Bevacizumab Added to Trastuzumab/Chemotherapy for Treatment of HER2+ Early Breast Cancer. SABCS 2013

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 2003–2014:**
**Bauerfeind / Blohmer / Dall / Fersis /
Göhring / Harbeck / Heinrich / Huober /
Jackisch / Kaufmann / Loibl / Lux / von
Minckwitz / Müller / Nitz / Schneeweiss /
Schütz / Solomayer / Untch**
- **Version 2015:**
Friedrich / Schneeweiss

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Subtype-specific General Systemic Strategies

AGO

++

- In case of indication for chemotherapy,
consider neoadjuvant approach

- **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
 - Plus Carboplatin in case of family history for BC/OC or gBRCA alteration

++

+

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

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- **Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy**
- **Pathological complete response is associated with improved survival in particular subgroups**
- **Can achieve operability in primary inoperable tumors**
- **Improved options for breast conserving surgery**
- **Allows individualization of therapy according to mid-course treatment effect**
- **Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery**

Oxford / AGO LoE / GR

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

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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**

**Oxford / AGO
LoE / GR**

2b B ++

1c A ++

1b B +

1b A +

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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 Therapy Response Prediction II

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Factor	LoE ₂₀₀₉	CTS	GR	AGO
➤ Multigene signature	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumour infiltrating lymphocytes	I	B	B	+
➤ <i>PIK3CA</i> mutation	II	B	B	+/-

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

Oxford / AGO LoE / GR

- **Standard regimens used in the adjuvant setting with a duration of at least 18 weeks**

1a A ++

- **AC or EC → D q3w or P q1w**

2b A ++

- **DAC**

2b B ++

- **AP → CMF**

1b A +

- **Taxane followed by anthracycline sequence**

1a A +

- **Dose-dense regimen (e.g. E -P-CMF, E-P-C)**

1b B +*

- **Platinum in TNBC**

1a A +/-

- **In case of family history of BC/OC or BRCA alteration**

2b B +

Superior Carboplatin Containing Regimens in the Neoadjuvant Setting

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Author	Study	Regimen	pCR rate
Sikov WM, et al. (JCO 2015)	CALGB 40603 Phase II	Paclitaxel 80mg/m ² qw x12 + Carboplatin AUC 6 q3w x4 – dd AC q2w x4	TNBC ± Cb: 54% vs 41% (ypT0/is ypN0)
von Minckwitz G, et al. (Lancet Oncol 2014)	Gepar Sixto Phase II	NPLD 20mg/m ² qw x18 + Paclitaxel 80mg/m ² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15mg/kg q3w x6	TNBC ± Cb: 53% vs. 37% (ypT0 ypN0)
Ando M, et al. (BCRT 2014)	Phase II	Paclitaxel 80mg/m ² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4	TNBC ± Cb: 61% vs. 26%

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Neoadjuvant Systemic Chemotherapy

Recommended Methods of Monitoring of Response

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- **Breast ultrasound**
- **Palpation**
- **Mammography**
- **MRI**
- **PET(-CT)**
- **Clip tumour region**

**Oxford / AGO
LoE / GR**

2b	B	++
2b	B	++
2b	B	++
2b	B	+
2b	B	+/-
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 | 1a | B | - |
| ➤ Lapatinib + Trastuzumab in combination with chemotherapy | 1a | B | +/- |
| ➤ Pertuzumab + Trastuzumab in combination with chemotherapy | 1a | B | + * |
| ➤ Two anti-HER2 agents without chemotherapy | 2b | B | +/- |
| ➤ Anti-HER2 agent in combination with endocrine treatment | 2b | C | +/- |

* Study participation recommended

Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Oxford / AGO
LoE / GR

Bevacizumab in combination with chemotherapy

➤ In hormone receptor positive BC

1b B -

➤ In TNBC

1b B +/-

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

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SLNB before or after NACT in cN0

SLNB before NACT
SLNB after NACT

2b
2a

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	2a 2b	B B	+/- +
		ycN+ (CNB/FNA)	ALND	2b	B	++

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Neoadjuvant Systemic Therapy

Indications for Mastectomy

Oxford / AGO
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** 2b 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 in Patients with Endocrine-responsive Breast Cancer

Oxford / AGO LoE / GR

➤ Postmenopausal patients:

➤ Who are inoperable
and can / will not receive chemotherapy

2a B +

➤ Optimizes the option for breast conserving therapy

1b A +

➤ Aromatase inhibitors (for > 3 months)

1a^a B +

➤ Aromatase inhibitor + lapatinib (HER2+ BC)

2b B +/-

➤ Premenopausal patients

➤ Who are inoperable
and can / will not receive chemotherapy

5 C +

➤ Tamoxifen

2b C +

➤ Aromatase inhibitors + LHRH

1b C +/-

➤ Concurrent chemo-endocrine therapy

1b A -

➤ Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status

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 and references:

Systematic review of published evidence:

PUBMED 1999-2015

ASCO 1999-2015

SABCS 1999-2015

ECCO/ESMO 1999-2015

Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information and references:

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Fisher B, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998; 16; 2672
2. Van der Hage JA, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001; 19; 4224
3. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26; 778
4. Gianni L et al. 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. J Clin Oncol 2009; 27; 2474

Pathological complete response is associated with improved survival in particular subgroups

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L et al. 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. J Clin Oncol 2009; 27; 2474
2. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011; 29; 3351
3. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30; 1796

4. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
5. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. J Clin Oncol 2014: 32; 3883
6. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Can achieve operability in primary inoperable tumors

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Makhoul I, et al. Neoadjuvant systemic treatment of breast cancer. J Surg Oncol 2011: 103; 348
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Improved options for breast conserving surgery

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Allows individualization of therapy according to mid-course treatment effect

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796

Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery

Abstimmungsergebnis der AGO-Empfehlungen: 9+, 14+/-, Rest Enthaltungen

1. Symmans WF, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; 25; 4414
2. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol* 2011; 29; 1956
3. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012; 30; 1796
4. Leone JP, et al. Sixteen years follow-up results of a randomized phase II trial of neoadjuvant fluorouracil, doxorubicin, and cyclophosphamide (FAC) compared with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in stage III breast cancer: GOCS experience. *Breast Cancer Res Treat* 2014; 143; 313
5. Berruti A, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: a meta-regression of 29 randomized prospective studies. *J Clin Oncol* 2014; 32, 3883
6. Abdel-Fatah TM, et al. Nottingham Clinico-Pathological Response Index (NPRI) after Neoadjuvant Chemotherapy (Neo-ACT) Accurately Predicts Clinical Outcome in Locally Advanced Breast Cancer. *Clin Cancer Res*. 2014 [Epub ahead of print]

Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information and references:

Inflammatory breast cancer

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Inoperable breast cancer

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011: 22; 515

Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

If similar postoperative adjuvant chemotherapy is indicated

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M, et al. Neoadjuvant chemotherapy: early response as a guide for further treatment: clinical, radiological, and biological. J Natl Cancer Inst Monogr 2011: 43; 138
2. Loibl S, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012: 13 ; 887

Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)

Further information and references:

Young age

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
2. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
3. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

cT1 / cT2 tumors o. N0 o. G3

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

4. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
5. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
6. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Negative ER and PgR status

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

7. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145

8. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
9. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Triple negative breast cancer (TNBC)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

10. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
11. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
12. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Positive HER2 status

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

13. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145
14. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. Breast Cancer Res Treat 2010: 124; 133
15. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. Breast Cancer Res Treat 2014: 144; 153

Non-lobular tumor type

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

16. Von Minckwitz G, et al. Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat 2011: 125; 145

17. Huober J, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res Treat* 2010: 124; 133
18. Loibl S, et al. Response and prognosis after neoadjuvant chemotherapy in 1,051 patients with infiltrating lobular breast carcinoma. *Breast Cancer Res Treat* 2014: 144; 153

Early clinical response

1. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012: 30; 1796

Neoadjuvant Systemic chemotherapy - Response Predictiong II (7/20)

Further information and references:

Multigene signature

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Denkert C, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol 2013: 24; 2786
2. Masuda H, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res 2013: 19; 5533-40

Ki-67

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Du Y, et al. The role of topoisomerase II α in predicting sensitivity to anthracyclines in breast cancer patients: a meta-analysis of published literatures. Breast Cancer Res Treat 2011: 129; 839
2. Denkert C, et al. Ki67 levels as predictive and prognostic parameters in pretherapeutic breast cancer core biopsies: a translational investigation in the neoadjuvant GeparTrio trial. Ann Oncol 2013: 24; 2786
3. Klauschen F, et al. Standardized Ki67 diagnostics using automated scoring - clinical validation in the GeparTrio breast cancer study. Clin Cancer Res 2014 [Epub ahead of print]

Tumour infiltrating lymphocytes

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Denkert C, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 28, 105, 2010
2. Mao Y, et al. The Value of Tumor Infiltrating Lymphocytes (TILs) for Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer: A Systematic Review and Meta-Analysis. PloS One 2014: 9; e115103

3. Miyshita M, et al. Tumor-infiltrating CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with pathological complete response to neoadjuvant chemotherapy. Breast Cancer Res Treat 2014: 148; 525

PIK3CA mutation

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Loibl S, et al. PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol 2014: 32; 3212
2. Sueta A, et al. An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. PloS One 2014: 9; e116054

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules (8/20 and 9/20)

Further information and references:

Standard regimens used in the adjuvant setting with a duration of at least 18 weeks

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

AC or EC → D q3w or P q1w

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Rastogi P, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26; 778
2. von Minckwitz G, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPARDUO study of the German Breast Group. J Clin Oncol 2005; 23; 2676

DAC

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008; 100; 542
2. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008; 100; 552

AP → CMF

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L, et al. Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. Clin Cancer Res 2005; 11; 8715

Taxane followed by anthracycline sequence

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Bines J, et al. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014; 25; 1079
2. Earl HM, et al. Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2×2 factorial randomised phase 3 trial. Lancet Oncol 2014; 15; 201

Dose-dense regimen (e.g. E -P-CMF, E-P-C)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M. et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J Clin Oncol 2009; 27; 2938
2. Untch M, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF versus a standard-dosed epirubicin/cyclophosphamide followed by paclitaxel ± darbepoetin alfa in primary breast cancer--results at the time of surgery. Ann Oncol 2011; 22; 1988
3. Untch M, et al. PREPARE trial: a randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel, and CMF versus a standard-dosed epirubicin-cyclophosphamide followed by paclitaxel with or without darbepoetin alfa in primary breast cancer--outcome on prognosis. Ann Oncol 2011; 22; 1999

Platinum in TNBC

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Alba E, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study. Breast Cancer Res Treat 2012: 136; 487
2. Von Minckwitz G , et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014: 15; 747
3. Ando M, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat 2014: 145; 401
4. Petrelli F, et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014: 144; 223
5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13

in case of family history of BC/OC or BRCA alteration

Abstimmungsergebnis der AGO-Empfehlungen: 21+, 3+/-

1. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 2014: 147; 401
2. Von Minckwitz et al. ASCO 2014 (abs 1005)

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information and references:

Breast ultrasound

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552

Palpation

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Mammography

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

MRI

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Javid S, et al. Can breast MRI predict axillary lymph node metastasis in women undergoing neoadjuvant chemotherapy. *Ann Surg Oncol* 2010; 17; 1841
2. Morrow M, et al. MRI for breast cancer screening, diagnosis, and treatment. *Lancet* 2011; 378; 1804
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol* 2012; 19; 1508

PET(-CT)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Dose-Schwarz J, et al. Assessment of residual tumour by FDG-PET: conventional imaging and clinical examination following primary chemotherapy of large and locally advanced breast cancer. *Br J Cancer* 2010; 102; 35
2. Coudert B, et al. Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and docetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and docetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): an open-label, randomised phase 2 trial. *Lancet Oncol* 2014; 15; 1493

Clip tumour region

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information and references:

Trastuzumab in combination with chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Buzdar AU, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 2007: 13; 228
2. 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 randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010: 375; 377
3. Untch M, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. J Clin Oncol 2010: 28; 2024
4. Pierga JY, et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. Breast Cancer Res Treat 2010: 122; 429-437
5. Untch M, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol 2011: 29; 3351
6. Von Minckwitz G, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012: 30; 1796
7. Cortazar P, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014: 384; 164
8. Gianni L, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet Oncol 2014: 15; 640

9. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014; 15; 1137

Lapatinib in combination with chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Untch M et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol* 2012; 13; 135 - 144
2. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14; 1183-1192
3. Alba E, et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *Br J Cancer* 2014; 110; 1139
4. Bonnefoi H, et al. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. *Ann Oncol* 2014 [Epub ahead of print]
5. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. *J Natl Cancer Inst* 2014; 106(9): [Epub ahead of print]

Lapatinib + Trastuzumab in combination with chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Robidoux A, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14; 1183-1192
2. De Azambuja E, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014; 15; 1137
3. Bonnefoi H, et al. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. *Ann Oncol* 2014 [Epub ahead of print]

4. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): [Epub ahead of print]

Pertuzumab + Trastuzumab in combination with chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012; 13; 25-32
2. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals Oncol 2013; 24; 2278-84
3. Nagayama A, et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106(9): [Epub ahead of print]

Two anti-HER2 agents without chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Gianni L, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012; 13; 25-32
2. Rimawi M, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. J Clin Oncol 2013; 31; 1726
3. Ismael G, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012; 13; 869

Anti-HER2 agent in combination with endocrine treatment

Abstimmungsergebnis der AGO-Empfehlungen: 3+, 16+/-, 6-

1. Rimawi MF, et al. SABCS 2014 (S6-02)
2. Guarneri V, et al. Double-blind, placebo-controlled, multicenter, randomized, phase IIb neoadjuvant study of letrozole-lapatinib in postmenopausal hormone receptor-positive, human epidermal growth factor receptor 2-negative, operable breast cancer. J Clin Oncol 2014; 32; 1050

Neoadjuvant Targeted Therapy in HER2 Negative Tumors (12/20)

Further information and references:

Bevacizumab in combination with chemotherapy in hormone receptor positive

Abstimmungsergebnis der AGO-Empfehlungen: 13+/-, 17-

1. Von Minckwitz G, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012: 366; 299
2. Bear HD, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012: 366; 310
3. Von Minckwitz G, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)[†]. Ann Oncol 2014: 25; 2363

Bevacizumab in combination with chemotherapy in TNBC

Abstimmungsergebnis der AGO-Empfehlungen: 2+/-, 13+/-, 9-

1. Von Minckwitz G, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012: 366; 299
2. Bear HD, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012: 366; 310
3. Gerber B, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). Annals Oncol 2013: 24; 2978
4. Von Minckwitz G, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)[†]. Ann Oncol 2014: 25; 2363
5. Sikov WM, et al. Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance). J Clin Oncol 2015: 33; 13

Neoadjuvant Systemic Therapy Procedures in Case of Early Response (13/20)

Further information and references:

In case of early response following 6 to 12 weeks of neoadjuvant chemotherapy:

Complete all chemotherapy before surgery i.e. ≥ 18 weeks of treatment

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001: 19; 3506
2. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542
3. Von Minckwitz G, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio study. J Natl Cancer Inst 2008: 100; 552
4. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response (14/20)

Further information and references:

In case of no change:

Completion of NST, followed by surgery

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508
2. Smith IC, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002: 20; 1456
3. Von Minckwitz G, et al. Neoadjuvant vinorelbine-capecitabine versus docetaxel-doxorubicin-cyclophosphamide in early nonresponsive breast cancer: phase III randomized GeparTrio trial. J Natl Cancer Inst 2008: 100; 542

Continuation of NST with non-cross-resistant regimen

AC or EC x 4 → D x 4 or Pw x 12

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Bear HD, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2003: 21; 4165
2. Bear HD, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006: 24; 2019

DAC x 2 → NX x 4

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Von Minckwitz G, et al. Response-guided neoadjuvant chemotherapy for breast cancer. J Clin Oncol. 2013; 31; 3623-30

In case of progressive disease:

Stop of NST and immediate surgery or radiotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

Additional adjuvant chemotherapy with non-cross-resistant regimen

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Mittendorf EA, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 29, 1956, 2011

Local/Regional Procedure after Neoadjuvant Systemic Therapy - Surgical Procedures (15/20 and 16/20)

Further information and references:

Mark previous tumor region

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Surgery

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Microscopically clear margins

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927

2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012: 19; 1508

Tumor resection in the new margins

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007: 18; 1927
2. Kaufmann M, et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010: 116; 1184
3. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer.. Ann Surg Oncol 2012: 19; 1508

Sentinel node biopsy (see chapter “Surgery”)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kühn T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013
2. Boughey JC et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013: 310; 1455-1461

Neoadjuvant Systemic Therapy - Indications for Mastectomy (17/20)

Further information and references:

Positive margins after repeated excisions

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508
2. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22; 515

Radiotherapy not feasible

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Kaufmann M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19; 1508

In case of clinical complete response:

Inflammatory breast cancer

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Dawood S, et al. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol 2011; 22; 515

Multicentric lesions

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014 [Epub ahead of print]

cT4a-c breast cancer

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ataseven B, et al. Impact of Multifocal or Multicentric Disease on Surgery and Locoregional, Distant and Overall Survival of 6,134 Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Ann Surg Oncol 2014 [Epub ahead of print]

Neoadjuvant Systemic - Therapy Timing of Surgery and Radiotherapy (18/20)

Further information and references:

Surgery after the nadir of the leucocyte count (2 to 4 weeks after last course of chemotherapy)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ring A, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003; 21; 4540

Radiotherapy after surgery 2–3 weeks after surgery BCS

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ring A, et al. Is surgery necessary after complete clinical remission following neoadjuvant chemotherapy for early breast cancer? J Clin Oncol 2003; 21; 4540
2. Daveau C, 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; 1452-145

Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment (19/20)

Further information:

Endocrine treatment in endocrine responsive disease

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Complete trastuzumab treatment for 1 year in HER2-positive disease

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

In case of insufficient response further chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Experimental therapies in clinical trials

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

No references

Neoadjuvant Endocrine Therapy (20/20)

Further information and references:

Postmenopausal patients:

Who are inoperable and can / will not receive chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244

Optimizes the option for breast conserving therapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001: 12; 1527
2. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005: 23; 5108
3. Semiglazov VF, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007: 110; 244
4. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009: 18; 339
5. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011: 29; 2342

Aromatase inhibitors (for > 3 months)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Eiermann W, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. Ann Oncol 2001; 12; 1527
2. Smith I, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005; 23; 5108
3. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339
4. Ellis MJ, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol 2011; 29; 2342

Aromatase inhibitor + lapatinib (HER2+ BC)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Premenopausal patients:

Who are inoperable and can / will not receive chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Tamoxifen

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Aromatase inhibitors + LHRH

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Concurrent chemo-endocrine therapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Mathew J, et al. Neoadjuvant endocrine treatment in primary breast cancer - review of literature. Breast 2009; 18; 339

2. Von Minckwitz G, et al. Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: a randomized, controlled, open phase IIb study. J Clin Oncol 2001; 15; 3506
3. Fontein DB, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. Eur J Cancer 2014; 50; 2190

Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Ellis MJ, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 2008; 100; 1380

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Adjuvant Radiotherapy

Adjuvant Radiotherapy (RT)

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➤ **Versions 2002–2014:**
**Souchon / Blohmer / Friedrichs / Göhring /
Janni / Möbus / Seegenschmiedt**

➤ **Version 2015:**
**Thomssen / Kühn / Untch / Scharl
Budach / Wenz / Souchon**

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Further
Information

References

Preliminary Note

- **The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between experts of the AGO and DEGRO**
- **For technical details of radiotherapy we recommend to refer to the corresponding updated DEGRO practical guidelines 2014**
- **If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue colour**

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): - Whole Breast Irradiation –

LoE 1b B

AGO ++

<40 years	Conventional RT (25-28 fractions) with integrated or sequential boost
40 – 65 years	Conventional RT with integrated or sequential boost, or hypofractionated RT with sequential boost
> 65 years	Low risk: consider hypofractionated RT without boost (15-16 fractions) High risk: RT as for 40-65 years
Elderly	Individual counseling including omission of radiotherapy according to individual risk after geriatric assessment
Any age (lymph node areas)	If radiotherapy of the regional lymph nodes is included, conventionally fractionated RT (25-28 fractions)

Study participation recommended

Additional Information with Regard to Effects of Breast Radiotherapy (BCT)

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➤ Hypofractionation:

- „Some normal tissue effects were less common after the 15 fraction regimen than the control schedule (breast shrinkage, telangiectasia, and breast oedema).“
- In 1 of 5 trials: “There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0.74, 95% CI 0.59–0.94), which contributed to the significantly higher rates of disease-free survival and overall survival in the 40 Gy group compared with the 50 Gy group.“ ($HR_{OS}=0.8$; $p=0.042$)
(*START B: Haviland JS et al. Lancet Oncol 2013; 14: 1086–94*)

➤ Elderly patients should be advised about the following :

- In older patients with pT1-2 ($=\leq 3$ cm) pN0 hormone receptor-positive breast cancer, breast irradiation for breast conserving therapy is able to reduce the risk of a local recurrence by about 8% over 10 years. A benefit with regard to metastasis-free survival and overall survival has not been found yet.

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Radiotherapy in Elderly Patient Life Expectancy less than 10 Years

Oxford / AGO
LoE / GR

- **Omission of radiotherapy in low risk* elderly patients if adjuvant endocrine treatment (e.g. Tam 5-yrs) is consequently performed***

AGO¹

1b A +

DEGRO¹

1b C +/-

**Increase in local recurrence,
no influence on OS, decrease in toxicity**

***Age ≥ 70 year, pT1, pN0, HR positive, G1-2, HER2-negative,
negative resection margin (width >1 mm)**

¹ different interpretation of published data by AGO and DEGRO

BCS $\geq 70y$ < 4 cm cN0: Tamoxifen vs. Tamoxifen + RT

Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

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@10 yrs (95% C.I.)	Tamoxifen	Tamoxifen plus Radiotherapy	Hazard Ratio
Local recurrence	90% (85%-93%)	98% (96%-99%)	HR=0.18 (95% CI, 0.07 to 0.42; $P < .001$)
Mastectomy- free	96% (93% - 98%)	98% (96% - 99%)	HR=0.50 (95% CI, 0.17 to 1.48; <i>n.s.</i>)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR=1.20 (95% CI, 0.63 to 2.32; <i>n.s.</i>)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR=0.95 (95% CI, 0.77 to 1.18; <i>n.s.</i>)

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Further
Information

References

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Hughes KE et al J Clin Oncol 2013; 31:2382-2387

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation

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	Oxford / AGO LoE / GR		
➤ Boost-RT (improves local control, no survival benefit)	1b	B	+
➤ < 40 years	1b	B	++
➤ 40-60 years	1b	B	++
➤ > 60 years, if G3 or >pT1	2b	B	+/-
➤ Intraoperative irradiation (IORT/IOERT)			
➤ As boost-irradiation followed by WBI	2a	B	+
➤ As sole radiotherapy modality			
➤ IORT using 50 kV (pT1 pN0 R0 G1-2, non-lobular, age >50 y, no extensive DCIS, IORT during first surgery, HR+)	1b	B	+/-*
➤ IOERT	1b	B	+/-*
➤ Postoperative partial breast irradiation as sole radiotherapy modality			
➤ Interstitial brachytherapy	1b	B	+/-*
➤ Intracavity balloon technique	2b	B	-*
➤ APBI (IMRT)**	2b	B	-*

* Study participation recommended; **no long term data

Boost vs no Boost: EORTC 22881-10882 Trial

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@20 yrs (95% C.I.)	Boost (n=2.661)	No boost (n=2.657)	Hazard Ratio (95% C.I.)
<u>Overall Survival</u> (Δ =-1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
<u>Cumulative Risk of Ipsilateral Breast Tumour Recurrence</u>			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p<0.0001
≤40 years (Δ =11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p=0.003
41–50 years (Δ =5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p=0.007
51–60 years (Δ =2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p=0.020
>60 years (Δ =3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p=0.019

(Median F/U 17.2 y)

acc. to: Bartelink et al. Lancet Oncol 2015; 16: 47–56

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Postmastectomy Radiotherapy (PMRT)** to the Chest Wall

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			Oxford / AGO LoE / GR		
➤	> 3 tumor infiltrated lymph nodes (Lnn.)		1a	A	++
➤	1–3 tumor infiltrated Lnn. high risk	AGO ¹	1a	A	+
➤	1–3 tumor infiltrated Lnn. low risk*	AGO ¹	5	D	+/-
➤	1–3 tumor infiltrated Lnn. (every risk)	DEGRO ¹	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	++
➤	➤ In young pts with high risk features		2b	B	++
➤	➤ After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)		2a	B	+
➤	➤ Omission of RT if ypT0 ypN0 after NACT**		2b	B	+/-
The indications for PMRT and regional RT are independent of adjuvant systemic treatment			1a	A	

¹ different interpretation of published data by AGO and DEGRO

*For definition of risk, go to Further information;

**Study participation recommended

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Radiotherapy of the Axilla

**Oxford / AGO
LoE / GR**

- **Tumor residuals after axillary dissection** **5 D ++**
- **Sentinel node negative** **1b B - -**
- **Axillary dissection not indicated e.g. cN0, SLN pos. (see chapter surgery)** **2a B -**
- **Extracapsular tumor spread (ECS)** **2b B - -**
- **Axillary micrometastases or isolated cells found in regional lymph nodes** **1b B - -**

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Axillary Intervention in Patients with Positive Sentinel Lymph Nodes

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Axillary dissection or RT of the axilla, if 1-2 pos. SLN:

- | | | | |
|--|----|---|------|
| ➤ BCT and ACOSOG Z011-criteria fulfilled | 1b | B | +/-* |
| ➤ No axillary treatment | 1b | B | +/- |
| ➤ BCT and ACOSOG Z011-criteria <u>not</u> met | 1b | B | ++* |
| ➤ Mastectomy, RT of chest wall indicated and ACOSOG Z011-criteria fulfilled | 5 | D | +/-* |
| ➤ No axillary treatment | 5 | D | +/- |
| ➤ Mastectomy, RT of chest wall indicated and ACOSOG Z011-criteria <u>not</u> met <i>or</i> Mastectomy, RT of chest wall <u>not</u> planned | 1b | D | ++ |

Axillary dissection or RT of the axilla, if ≥ 3 pos. SLN

- | | | | |
|------------------------------|----|---|----|
| ➤ Axillary dissection | 1b | B | ++ |
| ➤ Radiotherapy of the axilla | 1b | B | + |

*Study participation recommended

Radiotherapy (RT) of Other Locoregional Lymph Node Areas

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Supra-/infraclavicular lymphatic regions

		Oxford / AGO LoE / GR		
➤ ≥ pN2a		1b	A	++
➤ Level III involved		1b	A	++
➤ pN1a high risk*	AGO ¹	2b	B	+
➤ pN1a low risk*	AGO ¹	2b	B	+/-
➤ pN1a (every risk)	DEGRO ¹	2b	B	+
➤ pN0 high risk, if radiotherapy of the internal mammaria Inn. chain is indicated (see below)		2a	B	+/-
➤ After NACT/NAT (indications as for PMRT)	AGO ¹	2b	B	+/-
➤ After NACT/NAT if cN+ (indications acc. PMRT)	DEGRO ¹	2b	A	+

Internal mammaria lymph node region (IMC)

➤ pN1-pN2 and HR pos. who had systemic chemoth.	1b ^a	B	+
➤ pN0 high risk w. centr./med. tumors (HR+, adj.CT)	1b ^a	B	+/-
➤ IMC-RT, if cardiac risk factors are present <u>or</u> if trastuzumab is given	2b	A	--

¹ different interpretation of published data by AGO and DEGRO

*For definition of risk, go to Further information

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Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(median follow-up 10.9 yrs)

<u>Adjuvant treatment</u>	<u>n</u> *	<u>Hazard ratio</u> <u>(95%CI)</u>
No adjuvant reported	625	0.91 (0.59 - 1.39)
Chemotherapy	954	1.05 (0.84 - 1.32)
Endocrine therapy	1185	0.82 (0.63 - 1.06)
Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 – 0.94)
Total	4004	0.88 (0.76 – 1.01)

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013

Concomitant Use of Systemic Therapy with Radiotherapy

**Oxford / AGO
LoE / GR**

- **Trastuzumab* concurrent with radiotherapy** **2b B +**
- **Tamoxifen concurrent with radiotherapy** **2b B +**
- **AI (letrozole, anastrozole) concurrent with radiotherapy** **2b B +**

***in HER2 pos. tumors parasternal RT should generally be avoided;
no concurrent trastuzumab in parasternal RT**

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Adjuvant Radiotherapy – (2/15)

Further information:

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2015

References (Overviews):

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Lancet. 2014 Jun 21;383(9935):2127-35.

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.

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y, Peto R. Lancet. 2011 Nov 12;378(9804):1707-16.

Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast.

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, Wang Y, Clarke M, Davies C, Peto R, Bijker N, Solin L, Darby S. J Natl Cancer Inst Monogr. 2010;2010(41):162-77.

Preliminary Note (3/15)

Further information:

AGO – Arbeitsgemeinschaft für Gynäkologische Onkologie e.V.
DEGRO - Deutsche Gesellschaft für Radioonkologie e.V.

References:

DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer.

1. Wenz F, Sperk E, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Piroth MD, Sautter-Bihl ML, Sedlmayer F, Souchon R, Fussl C, Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2014 Aug;190(8):705-14.

DEGRO practical guidelines: radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways.

1. Sautter-Bihl ML, Sedlmayer F, Budach W, Dunst J, Feyer P, Fietkau R, Fussl C, Haase W, Harms W, Piroth MD, Souchon R, Wenz F, Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Strahlenther Onkol. 2014 Apr;190(4):342-51.

DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer.

1. 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). Strahlenther Onkol. 2013 Oct;189(10):825-33.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Whole Breast Irradiation (4/15)

Further information:

Basically, data on hypofractionation in PMRT and BCT are valid for all subgroups and age groups. However, for concerns with long term toxicity (data are not yet sufficient), hypofractionation is opened for specific patient groups as recommended in this slide. Although some data showed that also integration of boost irradiation into hypofractionation protocol is feasible, it is not accepted as a standard.

Treatment of these patients in ongoing clinical trials is recommended.

References:

1. Haviland JS¹, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013 Oct;14(11):1086-94.
2. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med.* 2010 Feb 11;362(6):513-20.
3. Haffty BG¹, Buchholz TA. Hypofractionated breast radiation: preferred standard of care? *Lancet Oncol.* 2013 Oct;14(11):1032-4.
4. Hopwood P¹, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR; START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol.* 2010 Mar;11(3):231-40.

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6. Bane AL¹, Whelan TJ, Pond GR, Parpia S, Gohla G, Fyles AW, Pignol JP, Pritchard KI, Chambers S, Levine MN. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. *Ann Oncol.* 2014 May;25(5):992-8.
7. Chan EK1, Woods R2, McBride ML2, Virani S3, Nichol A4, Speers C5, Wai ES4, Tyldesley S6. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-stage breast cancer: long-term hospital-related morbidity from cardiac causes. *Int J Radiat Oncol Biol Phys.* 2014 Mar 15;88(4):786-92.
8. Freedman GM, White JR, Arthur DW, Allen Li X, Vicini FA. Accelerated fractionation with a concurrent boost for early stage breast cancer. *Radiother Oncol.* 2013 Jan;106(1):15-20.

Additional Information with Regard to Effects of Breast Radiotherapy (BCT) (5/15)

Further information:

Additional information with regard to effects of radiotherapy in breast conservation (BCT)

Hypofractionation:

„Some normal tissue effects were less common after the 15 fraction regimen than the control schedule (breast shrinkage, telangiectasia, and breast oedema).“

In 1 of 5 trials: “There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0.74, 95% CI 0.59–0.94), which contributed to the significantly higher rates of disease-free survival and overall survival in the 40 Gy group compared with the 50 Gy group.“ ($HR_{OS}=0.8$; $p=0.042$)

START B: Haviland JS et al. Lancet Oncol 2013; 14: 1086–94

Elderly patients should be counseled about:

Absolute benefit of WBRT in older women with pT1-2 (up to 3 cm) pN0, HR-positive breast cancer after BCS and endocrine therapy is small (2-8 % after ten yrs) and decreases with increasing age. No advantage with regard to secondary mastectomy, metastasis-free survival and overall survival has been observed.

References:

1. Haviland JS¹, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 2013 Oct;14(11):1086-94.

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3. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015 Jan 27.
4. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? *The Lancet Oncology*, Available online 28 January 2015

Radiotherapy in Elderly Patient Life Expectancy less than 10 Years (6/15)

Further information:

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs.;

We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival, and the biology of the tumor dictates the rate of IBTR, not the length of life.

References:

1. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, Muss HB, Smith BL, Hudis CA, Winer EP, Wood WC. 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 Jul 1;31(19):2382-7.
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3. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? The Lancet Oncology, Available online 28 January 2015

BCS ≥ 70 y <4 cm cN0: Tamoxifen vs. Tamoxifen + RT (7/15)

Further information:

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs.

We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival; the biology of the tumor dictates the rate of IBTR, not the length of life.

Reference:

1. Hughes KS, Schnaper LA, Bellon JR, Cirincione CT, Berry DA, McCormick B, Muss HB, Smith BL, Hudis CA, Winer EP, Wood WC. 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 Jul 1;31(19):2382-7.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation (8/15)

Further information:

The primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0.09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer.

Reference:

1. Bartelink et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Supplementary appendix. Lancet Oncol 2014; published online Dec 9. [http://dx.doi.org/10.1016/S1470-2045\(14\)71156-8](http://dx.doi.org/10.1016/S1470-2045(14)71156-8).

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Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Partial Breast Irradiation - Boost-RT (improves local control, no survival benefit) (LoE 1a A AGO+)

1. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagl D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients

treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.
Lancet Oncol. 2015 Jan;16(1):47-56.

Boost-RT in pts <40 years (LoE 1b A AGO++)

Boost-RT in pts 40-60 years (LoE 1b B AGO+)

1. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagel D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015 Jan;16(1):47-56.

Boost-RT in pts >60 years, if G3 or >T1 (LoE 2b B AGO+/-)

Antonini et al. Radiotherapy and Oncology 82 (2007) 265–271

Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI (LoE 2a B AGO+)

1. IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: long term results of an ISIIORT pooled analysis. Fastner G, Sedlmayer F, Merz F, Deutschmann H, Reitsamer R, Menzel C, Stierle C, Farmini A, Fischer T, Ciabattini A, Mirri A, Hager E, Reinartz G, Lemanski C, Orecchia R, Valentini V. Radiother Oncol. 2013 Aug;108(2):279-86.
2. IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer--results of a case series after 5-year follow-up. Fastner G, Reitsamer R, Ziegler I, Zehentmayr F, Fussl C, Kopp P, Peintinger F, Greil R, Fischer T, Deutschmann H, Sedlmayer F. Int J Cancer. 2015 Mar 1;136(5):1193-201.

3. Ann Surg Oncol. 2010 Oct;17 Suppl 3:352-8. doi: 10.1245/s10434-010-1265-z. Single-center long-term follow-up after intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage x-rays. Blank E¹, Kraus-Tiefenbacher U, Welzel G, Keller A, Bohrer M, Sütterlin M, Wenz F.

As sole radiotherapy modality

IORT using 50 kV (pT1 pN0 R0 G1-2, non-lobular, age >50 y, no extensive DCIS, IORT during first surgery, HR+) (LoE 1b B AGO+/-)

1. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. Lancet. 2010 Jul 10;376(9735):91-102.
2. Lancet. 2014 Feb 15;383(9917):603-13. 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. Vaidya JS¹, Wenz F², Bulsara M³, Tobias JS⁴, Joseph DJ⁵, Keshtgar M⁶, Flyger HL⁷, Massarut S⁸, Alvarado M⁹, Saunders C¹⁰, Eiermann W¹¹, Metaxas M¹², Sperk E², Sütterlin M¹³, Brown D¹⁴, Esserman L⁹, Roncadin M¹⁵, Thompson A¹⁴, Dewar JA¹⁶, Holtveg HM⁷, Pigorsch S¹⁷, Falzon M¹⁸, Harris E¹⁹, Matthews A²⁰, Brew-Graves C¹², Potyka I¹², Corica T⁵, Williams NR¹², Baum M¹²; TARGIT trialists' group.

IOERT as sole radiotherapy modality (LoE 1b B AGO+/-)

1. Lancet Oncol. 2013 Dec;14(13):1269-77. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Veronesi U¹, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrada S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B.

Postoperative partial breast irradiation as sole radiotherapy modality
Interstitial brachytherapy (LoE 1b B AGO+/-)

1. Aristei C, Palumbo I, Capezzali G, et al. Outcome of a phase II prospective study on partial breast irradiation with interstitial multi-catheter highdose rate brachytherapy. *Radiother Oncol* 2013;108:236-241.

Intracavity balloon technique (LoE 1b B AGO-)

1. *Am J Surg.* 2007 Oct;194(4):456-62. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. Benitez PR¹, Keisch ME, Vicini F, Stolier A, Scroggins T, Walker A, White J, Hedberg P, Hebert M, Arthur D, Zannis V, Quiet C, Streeter O, Silverstein M.

APBI (IMRT) (LoE 1b B AGO-*)

1. Lehman M, Hickey BE, Francis DP, See AM. Partial breast irradiation for early breast cancer. *Cochrane Database Syst Rev.* 2014 Jun 18;6:CD007077.
2. *Eur J Cancer.* 2015 Jan 17. pii: S0959-8049(15)00002-7. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Livi L¹, Meattini I², Marrazzo L³, Simontacchi G¹, Pallotta S³, Saieva C⁴, Paiar F¹, Scotti V¹, De Luca Cardillo C¹, Bastiani P⁵, Orzalesi L⁶, Casella D⁶, Sanchez L⁶, Nori J⁷, Fambrini M⁸, Bianchi S⁹.
3. *J Clin Oncol.* 2013 Nov 10;31(32):4038-45. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. Olivetto IA¹, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, Kong I, Cochrane B, Nichol A, Roy I, Germain I, Akra M, Reed M, Fyles A, Trotter T, Perera F, Beckham W, Levine MN, Julian JA.

Boost vs no Boost: EORTC 22881-10882 Trial (9/15)

Further information:

Primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0.09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer.

Reference:

1. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagel D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol.* 2015 Jan;16(1):47-56.
2. Bartelink et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Supplementary appendix. *Lancet Oncol* 2014; published online Dec 9. [http://dx.doi.org/10.1016/S1470-2045\(14\)71156-8](http://dx.doi.org/10.1016/S1470-2045(14)71156-8).

Postmastectomy Radiotherapy (PMRT) to the Chest Wall (10/15)**

Further information:

The interpretation of the current EBCTCG publication (2014) should take into account, that this meta-analysis is highly influenced by the Danish radiotherapy trials (Overgaard et al. 1997, 1999).

Strong evidence on definition of low risk criteria with regard to the group of 1-3 tumor infiltrated axillary Lnn is lacking. Different definitions are discussed eg.

Kyndi et al. 2013: Low risk of locoregional recurrence, if at least 3 out of 4 favourable criteria are present:

- Hormone receptor receptor status positive,
- Grad I,
- HER2 negative,
- Tumor <2 cm).

Truong et al. 2005: High risk of locoregional recurrence

- If younger age (<45 yrs; HR=3.44) and one of the following factors:
 - High proportion of positive nodes (>25%; HR=2.00),
 - Medial tumour location (HR=2.46) or
 - Negative ER-Status (HR=2.02) and,
- If age 45+ yrs and
 - high proportion of positive nodes (>25%).

Also Grading (G3) and vessel invasion, are sometimes considered as criteria of high risk for locoregional recurrence.

However, from the current literature a unique definition cannot be concluded. Since EBCTCG overview demonstrates a broad benefit in patients with 1-3 tumor infiltrated axillary lymph nodes, the NCCN guidelines are stating: “Strongly consider postchemotherapy radiation therapy to chest wall plus infraclavicular and supraclavicular areas; if radiation therapy is given, strongly consider internal mammary node radiation therapy.”

References:

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014 Jun 21;383(9935):2127-35.
2. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, Kjaer M, Gadeberg CC, Mouridsen HT, Jensen MB, Zedeler K. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med*. 1997 Oct 2;337(14):949-55.
3. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, Kamby C, Kjaer M, Gadeberg CC, Rasmussen BB, Blichert-Toft M, Mouridsen HT. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*. 1999 May 15;353(9165):1641-8.
4. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005 Apr 1;61(5):1337-47.
5. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg*. 2013 Sep 11;2013:212979.
6. Kyndi M, Overgaard M, Nielsen HM, Sørensen FB, Knudsen H, Overgaard J. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol*. 2009 Jan;90(1):74-9.
7. NCCN Guidelines for Treatment of Cancer by Site
“http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast” download 2014

References according to the statements:

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.) (LoE1a A AGO++):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) high risk (LoE 1a A AGO+):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet*. 1999 May 15;353(9165):1641-8.

5. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005 Apr 1;61(5):1337-47.
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8. NCCN Guidelines for Treatment of Cancer by Site
“http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast” download 2014

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) low risk (LoE 5 D AGO+/-):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014 Jun 21;383(9935):2127-35.
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[“http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast”](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast) download 2014

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer (LoE 1a A AGO++):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors) LoE 2b B AGO+/-):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014 Jun 21;383(9935):2127-35.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor) (LoE 1a A AGO++):

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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3. Truong PT, Olivotto IA, Speers CH, Wai ES, Berthelet E, Kader HA. A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. Int J Radiat Oncol Biol Phys. 2004 Mar 1;58(3):797-804.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features (LoE 2b B AGO++):

1. Garg AK, Oh JL, Oswald MJ, et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. Int J Radiat Oncol Biol Phys 2007; 69: 1478-83.

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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. after neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d) (LoE 2a A AGO+):

1. Wright JL, Takita C, Reis IM, Zhao W, Saigal K, Wolfson A, Markoe A, Moller M, Hurley J. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer*. 2013 Jan 1;119(1):16-25.
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3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012 Jun;13(6):e270-6.

Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT (LoE 2b B AGO+/-):

1. Wright JL, Takita C, Reis IM, Zhao W, Saigal K, Wolfson A, Markoe A, Moller M, Hurley J. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer*. 2013 Jan 1;119(1):16-25.
2. Huang EH, Tucker SL, Strom EA, McNeese MD, Kuerer HM, Buzdar AU, Valero V, Perkins GH, Schechter NR, Hunt KK, Sahin AA, Hortobagyi GN, Buchholz TA. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol*. 2004 Dec 1;22(23):4691-9.
3. Hoffman KE, Mittendorf EA, Buchholz TA. Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy. *Lancet Oncol*. 2012 Jun;13(6):e270-6.

Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment (LoE 1a A)

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014 Jun 21;383(9935):2127-35.

Further references:

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials.

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Lancet. 2014 Jun 21;383(9935):2127-35.

DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer.

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Radiotherapy of the Axilla (11/15)

No further information

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References related to the statements:

Tumor residuals after axillary dissection (LoE 2b B, AGO ++)

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL Leitlinie. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.

Sentinel node negative (LoE 1b B, AGO --)

1. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Scarth HMC, Wolmark N. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABPB-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927–33.
2. Helms G, Kuhn T, Moser L, Remmel E, Kreienberg R. Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection: data from a prospective randomised trial. Eur J Surg Oncol 2009; 35: 697–701.
3. Kuehn T, Bembenek A, Decker T, et al, for the Consensus Committee of the German Society of Senology. A concept for the clinical implementation of sentinel lymph node biopsy (SLNB) in breast cancer patients with special regard to quality assurance. Cancer 2005; 103: 451–61.

4. Lyman GH, Giuliano AE, Somerfeld MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. *J Clin Oncol* 2005; 23: 7703–20.
5. Galimberti V, Manika A, Maisonneuve P, Corso G, Salazar Moltrasio L, Intra M, Gentilini O, Veronesi P, Pagani G, Rossi E, Bottiglieri L, Viale G, Rotmensz N, De Cicco C, Grana CM, Sangalli C, Luini A. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. *Eur J Surg Oncol*. 2014 Oct;40(10):1203-8.

Axillary dissection not indicated e.g. cN0, SLN positive (see surgical chapter) (LoE 2a B, AGO -)

1. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis. A Randomized Clinical Trial. *JAMA*. 2011;305(6):569-575

Extracapsular tumor spread (ECS) (LoE 2b B, AGO --)

1. Stranzl H, Ofner P, Peintinger F. Postoperative irradiation in breast cancer patients with one to three positive axillary lymph nodes. Is there an impact of axillary extranodal tumor extension on locoregional and distant control? *Strahlenther Onkol*. 2006 Oct;182(10):583-8.
2. Stranzl H, Mayer R, Ofner P, Peintinger F, Prettenhofer U, Hackl A. Extracapsular extension in positive axillary lymph nodes in female breast cancer patients. Patterns of failure and indications for postoperative locoregional irradiation. *Strahlenther Onkol*. 2004 Jan;180(1):31-7.

Axillary micrometastases or isolated cells found in regional lymph nodes (LoE 3b B, AGO --)

1. Pernas S1, Gil M, Benítez A, Bajen MT, Climent F, Pla MJ, Benito E, Guma A, Gutierrez C, Pisa A, Urruticoechea A, Pérez J, Gil Gil M. Avoiding axillary treatment in sentinel lymph node micrometastases of breast cancer: a prospective analysis of axillary or distant recurrence. *Ann Surg Oncol*. 2010 Mar;17(3):772-7.

2. Yegiyants S, Romero LM, Haigh PI, DiFronzo LA. Completion axillary lymph node dissection not required for regional control in patients with breast cancer who have micrometastases in a sentinel node. Arch Surg. 2010 Jun;145(6):564-9.

Axillary Intervention in Patients with Positive Sentinel Lymph Nodes (12/15)

Further information:

The optimal management of patients with a positive axillary lymph node status (pSN1) remains unclear. Future studies (e.g. INSEMA) are urgently needed.

References related to the statements:

1-2 pos SLN: BCT: no further treatment to the Axilla (criteria according ACOSOG Z011) (LoE 1b B, AGO+/-)

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
2. Galimberti V1, Cole BF, Zurrada S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305.
3. Jagsi R, Manjoet C, Moni J, Ballmann K, Laurie F, Buchholz TA, Giuliano A, Haffty BG. Radiation field design in the ACOSOG Z0011 (Alliance) trial. J Clin Oncol 2014;Nov 10;32(32): 3600-6

1-2 pos SLN: BCT: Axillary dissection (LoE 1b B, AGO +/-)

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
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1-2 pos SLN: BCT: radiotherapy of the axilla (LoE 1b B, AGO +/-)

1. Donker M, Tienhoven G, Straver ME, Meijnen P, van der Velde JH, Mansel RE, Catagliotti C, Westenburg AH, Klinkenbigt JHG, Orzalesi L, Boum WH, van der Mijte HCG, Nienwerhuijzen GAP, Keltkamp SC, Staets L, Duez NJ, de Graf PW, van Daten T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10

1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, axillary dissection or radiotherapy of the axilla (LoE 1b B, AGO +)

1. Donker M, Tienhoven G, Straver ME, Meijnen P, van der Velde JH, Mansel RE, Catagliotti C, Westenburg AH, Klinkenbigt JHG, Orzalesi L, Boum WH, van der Mijte HCG, Nienwerhuijzen GAP, Keltkamp SC, Staets L, Duez NJ, de Graf PW, van Daten T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.

1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, no axillary treatment (criteria ACOSOG Z011) (LoE 5 D, AGO+/-)

EXPERT OPINION, extrapolated from:

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-5753.
2. Galimberti V1, Cole BF, Zurrada S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U; International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305.

1-2 pos SLN: Mastectomy: If RT of chestwall is not planned, axillary dissection or radiotherapy of the axilla (LoE 5 AGO++)

EXPERT OPINION, extrapolated from:

1. Donker M, Tienhoven G, Straver ME, Meijnen P, van der Velde JH, Mansel RE, Catagliotti C, Westenburg AH, Klinkenbigt JHG, Orzalesi L, Boum WH, van der Mijte HCG, Nienwerhuijzen GAP, Keltkamp SC, Staets L, Duez NJ, de Graf PW, van Daten T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.

>=3 positive SLN: Axillary LN dissection (LoE 1b B, AGO ++)

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
2. Donker M, Tienhoven G, Straver ME, Meijnen P, van der Velde JH, Mansel RE, Catagliotti C, Westenburg AH, Klinkenbigt JHG, Orzalesi L, Boum WH, van der Mijte HCG, Nienwerhuijzen GAP, Keltkamp SC, Staets L, Duez NJ, de Graf PW, van Daten T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.
3. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.

>=3 positive SLN: Radiotherapy of the axilla (LoE 1b B, AGO +)

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-575.
2. Donker M, Tienhoven G, Straver ME, Meijnen P, van der Velde JH, Mansel RE, Catagliotti C, Westenburg AH, Klinkenbigt JHG, Orzalesi L, Boum WH, van der Mijte HCG, Nienwerhuijzen GAP, Keltkamp SC, Staets L, Duez NJ, de Graf PW, van Daten T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JWS, Belkacemi Y, Petignat P, Schinagl DAX, Coens C, Messina CGM, Bogaerts J, Rutgers EJT. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS) a randomised, multicenter open label, phase 3 non inferiority trial. Lancet Oncol 2014;15:1333-10.

3. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014 Jun 21;383(9935):2127-35.

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (13/15)

Further information:

The **definition of high risk and low risk pN1a** is different with regard to that in PMRT and that in RT of supra- and infraclavicular lymphatic regions. A proposal by Yates et al. assigns patients as following:

Low risk, if the following conditions are given: G1 with 1-3 positive LN; or G2 with 2 positive LN; **or** G3 plus 1 positive LN (10 years supraclavicular recurrence rate <10%).

High risk if the following conditions are given: G3 plus 2-3 positive LN; **or** G2 plus 3 positive LN (10 years supraclavicular recurrence rate 21%).

References:

1. Yates L, Kirby A, Crichton S, Gillett C, Cane P, Fentiman I, Sawyer E. Risk factors for regional nodal relapse in breast cancer patients with one to three positive axillary nodes. Int J Radiat Oncol Biol Phys. 2012 Apr 1;82(5):2093-103.
2. Viani GA, Godoi da Silva LB, Viana BS. Patients with N1 breast cancer: who could benefit from supraclavicular fossa radiotherapy? Breast. 2014 Dec;23(6):749-53.

References related to the statements:

Supra-/infraclavicular lymphatic regions

RT to Supra-/infraclavicular lymphatic regions if \geq pN2a (LoE 1b A; AGO++)

1. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
2. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.
3. P. F. Nguyen-Tan, L. Vincent, F. Methot et al., "The incidence of supraclavicular failure in patients with T1-2 breast cancer an four or more positive nodes treated by conservative surgery and tangential breast irradiation without regional nodal irradiation," International Journal of Radiation Oncology Biology Physics, vol. 42, supplement 1, p. 249, 1998.

RT to Supra-/infraclavicular lymphatic regions if Level III involved (LoE 1b A; AGO ++)

1. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
2. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.

RT to Supra-/infraclavicular lymphatic regions if pN1a high risk (LoE 2b B; AGO+)

1. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
2. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.

RT to Supra-/infraclavicular lymphatic regions if pN1a low risk (LoE 2b B; AGO+/-)

1. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
2. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.

RT to Supra-/infraclavicular lymphatic regions if pN0 high risk, if radiotherapy of the internal mammae chain is indicated (see below) (LoE 2a B; AGO+/-)

1. Whelan TJOI, Ackerman I, Chapman JW, Chua B, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Craighead P, Nolan MC, Bowen J, McCready DR, Pritchard KI, Leine MN, Parulekar W, Parulekar W: NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol ASCO Annual Meeting Proceed (Post-Meeting Edition) 2011:29.
2. Budach W, Kammers K, Boelke E, Matuschek C. Adjuvant radiotherapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials. Radiat Oncol. 2013 Nov 14 ;8:267.

RT to Supra-/infraclavicular lymphatic regions after NACT/NAT (indications as for PMRT) (LoE 2b B; AGO+/-)

1. Bernier J. Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer patients: A review. Crit Rev Oncol Hematol. 2015 Mar;93(3):180-189.
2. Mamounas EP, Anderson SJ, Dignam JJ, Bear HD, Julian TB, Geyer Jr CE, 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.
3. Buchholz TA, Tucker SL, Masullo L, Kuerer HM, Erwin J, Salas J, et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol 2002;20:17-23.

Internal mammaia lymph node region (IMC)

RT to Internal mammaia lymph node region (IMC) if pN1-pN2 and HR positive in patients who had systemic chemotherapy 1b^a B +

1. Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, Carrie C, Roullet B, Suchaud JP, Teissier E, Lucardi A, Gerard JP, Belot A, Iwaz J, Ecochard R, Romestaing P. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. Int J Radiation Oncol Biol Phys 2013; 86 (5): 860-866.
2. Chang JS, Park W, YB Kim, 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 Radiation Oncol Biol Phys, 2013; 86 (5): 867-872.
3. Poortmans PSH, Kirkove C, Budach V, Maingon P, Valli MC, Collette S, Fourquet A, Bartelink H, Van den Bogaert W: 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. EJC 2013, 47(Suppl 2).
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.

RT to Internal mammaia lymph node region (IMC) if pN0 high risk with central/medial tumors 1b^a B +/-

1. Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, Carrie C, Roullet B, Suchaud JP, Teissier E, Lucardi A, Gerard JP, Belot A, Iwaz J, Ecochard R, Romestaing P. Ten-Year Survival Results of a Randomized Trial of Irradiation of Internal Mammary Nodes After Mastectomy. Int J Radiation Oncol Biol Phys 2013; 86 (5): 860-866.
2. Chang JS, Park W, YB Kim, 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 Radiation Oncol Biol Phys, 2013; 86 (5): 867-872.

3. Poortmans PSH, Kirkove C, Budach V, Maingon P, Valli MC, Collette S, Fourquet A, Bartelink H, Van den Bogaert W: 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. EJC 2013, 47(Suppl 2).
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.

Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes (14/15)

No further information

References:

1. Poortmans P, Struikmans H, Kirkove C, Budach V, Maingon P, Valli MC, Collette L, Fourquet A, Bartelink H, Van den Bogaert W. 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): abstr. #2BA.

Concomitant Use of Systemic Therapy with Radiotherapy (15/15)

No further information

References:

Trastuzumab* concurrent with radiotherapy (LoE2b B AGO+) (*in HER2 pos tumors parasternal RT should generally be avoided;

no concurrent trastuzumab in parasternal RT)

1. 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).
2. 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.
3. Chung C, Stuart D, Keves M. Radiation recall reaction induced by adjuvant trastuzumab (Herceptin). Case Report Med 2009;2009:307894.
4. 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.
5. 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.
6. Jacob J, Belin L, Pierga JY, Gobillion A, Vincent-Salomon A, Dendale R, Beuzeboc P, Campana F, Fourquet A, Kirova YM. Concurrent administration of trastuzumab with locoregional breast radiotherapy: long-term results of a prospective study. Breast Cancer Res Treat. 2014 Nov;148(2):345-53.
7. 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.

8. 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

Tamoxifen concurrent with radiotherapy (LoE 2b B AGO +)

1. Chargari C¹, Toillon RA, Macdermed D, Castadot P, Magné N. Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? *Lancet Oncol*. 2009 Jan;10(1):53-60.
2. 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.
3. Recht A. Radiotherapy, antihormonal therapy, and personalised medicine. *Lancet Oncol* 2010;11:215-216.
4. 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
5. 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.

AI (letrozole, anastrozole) concurrent with radiotherapy (LoE 2b B AGO +)

1. Chargari C¹, Toillon RA, Macdermed D, Castadot P, Magné N. Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? *Lancet Oncol*. 2009 Jan;10(1):53-60.
2. 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
3. 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
4. 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.

5. 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.
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Other compounds (bevacizumab)

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Therapy Side Effects

START

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- **Versions 2004–2014:**
**Albert / Bischoff / Brunnert / Costa /
Friedrich / Friedrichs / Gerber / Göhring
/ Huober / Jackisch/ Lisboa / Müller /
Nitz / Schmidt / Souchon / Stickeler /
Untch**

- **Version 2015:**
Lück/Dall

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Toxicity Assessment

Acute Toxicity According to WHO¹ or NCI-CTC²

Grade	Information required
0 none	organs involved
1 mild	type of toxicity
2 moderate	time interval after treatment
3 severe	effect on general health status
4 life threatening	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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	Allergy	Bladder	Neuro- toxi	Cutane Tox	Diarrhea	
Cyclophosphamide	+	+	+	+		
Methotrexate	+		+	++		
5-Fluorouracil				+	+	
Carboplatin						
Cisplatin			+++			
Capecitabine				++	++	
Gemcitabine						Flue-like Synd., Edema
Epi-/Doxorubicin	+					Paravasate, Dextraxozane
Liposomal Doxo.	+			+		
Pegliposomal Doxo.	+			+++		
Mitoxantrone						
Paclitaxel	+++		++		+	Myalgia
nab-Paclitaxel	+		++		+	Myalgia
Docetaxel	++		+	++	+	Myalgia, Fluid retention, nails!
Vinorelbine			++			Thrombophlebitis, Obstipation
Eribulin				++		

ASCO Guidelines PNP

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ASCO SPECIAL ARTICLE

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Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn Hershman, Columbia University Medical Center, New York; Robert Dworkin, University of Rochester, Rochester, NY; Christina Lacchetti and Kate Bak, American Society of Clinical

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstriep, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi

Recommendations:

On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine. Although the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions given the limited other CIPN treatment options. Further research on these agents is warranted.

J Clin Oncol 32:1941-1967. © 2014 by American Society of Clinical Oncology

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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**

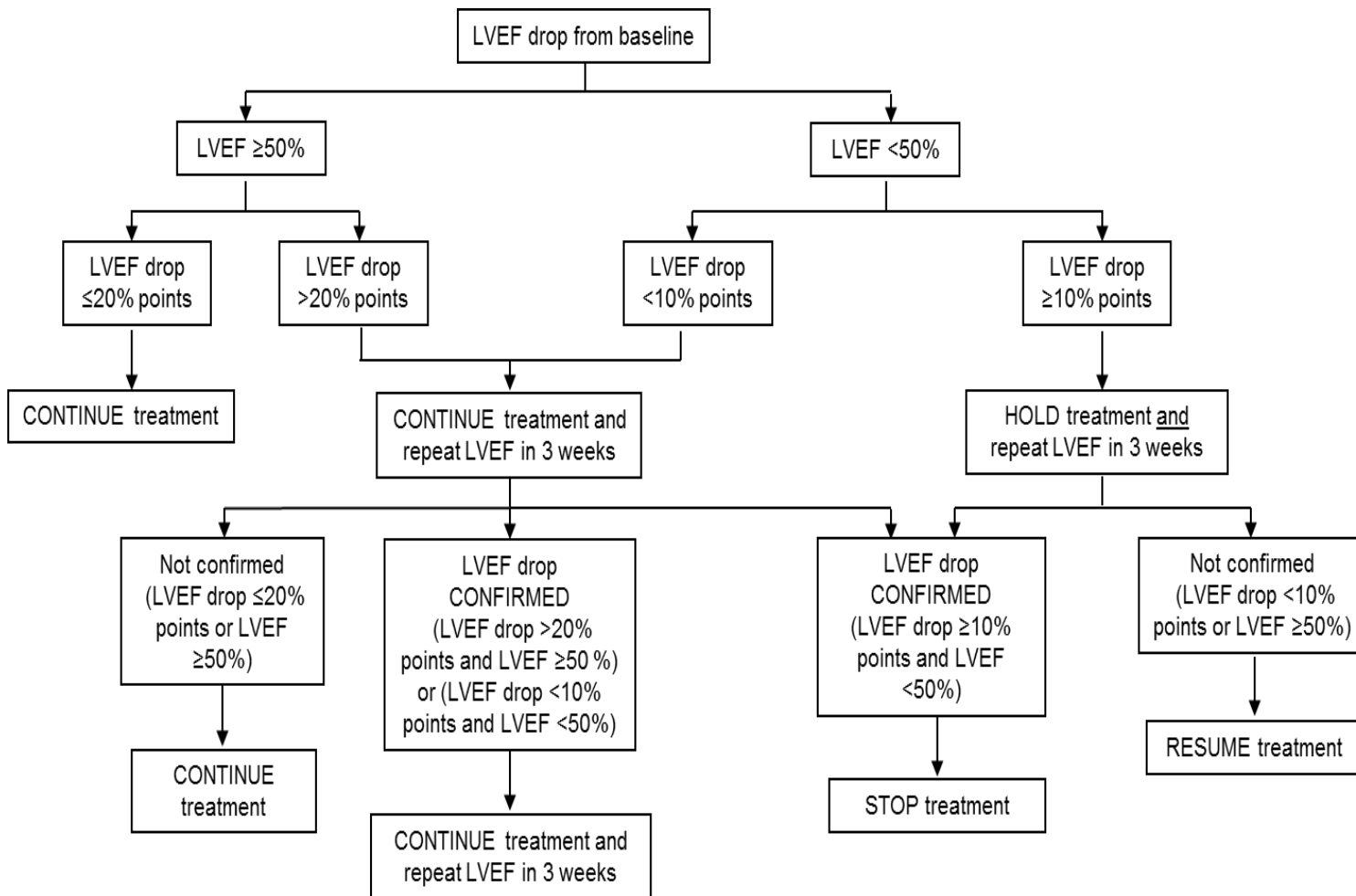
Regarding cardiac toxicity

➤ 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**
- **PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5-1%**
- **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

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%)**
- **Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue**
- **Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue**
- **Physical exercise with ambiguous effects regarding fatigue**
- **Methylphenidate might improve fatigue**

2a B

1a A ++

1a A ++

1b D +

1a D +

(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 – Antibodies / Antibody-drug-conjugates

Oxford / AGO
LoE / GR

Trastuzumab

- **Cardiotoxicity in the adjuvant setting (0,8–4,0%)**
- **Troponin I might identify patients who are at risk for cardiotoxicity**

1b A

2b B

Bevacizumab

- **Hypertonus, proteinuria, bleeding, left ventricular dysfunction,**

1a A

Pertuzumab

- **Skin rash, diarrhea, mucositis**

2b B

T-DM1

- **Thrombocytopenia, hepatotoxicity pyrexia, headache, pneumonitis**

2b B

Small Molecules

Oxford / AGO
LoE / GR

Lapatinib

- Diarrhea, skin rash, fatigue

1b A

Everolimus

- Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, Thrombocytopenia

2b B

PARP-inhibitors (olaparib)

- Fatigue, myelosuppression

3 C

cdk4/6 inhibitors (palbociclip, LEE011)

- myelosuppression, neutropenia

3 C

Therapy Side Effects (2/22)

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 (3/22)

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 (4/22)

No further information

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Cytotoxic Anti-Cancer Drugs – Acute Toxicity II (5/22)

No further information

References:
see slide 4

ASCO Guidelines PNP (6/22)

No further information

No references

Long-Term Toxicity Cardiotoxicity I (7/22)

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 af 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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Statements

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Feasibility of Treatment Combinations Considering Toxicities (8/22)

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 (9/22)

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 (10/22)

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 (11/22)

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) (12/22)

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 (13/22)

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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(Therapy Associated) Sleeping disturbance (14/22)

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 (15/22)

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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(Therapy Associated) Cognitive Impairment (16/22)

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 (17/22)

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) (18/22)

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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Acute phase rea

Gastrointestinal side effects...

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Recommendations for Precautions to Prevent ONJ (19/22)

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 Bone Modifying Agents (BMA) (20/22)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 18-19/22!

Key-Toxicities Antibodies/Antibody-drug-conjugates – Small Molecules (21/22) and (22/22)

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 bvacizumab 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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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Supportive Care

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Further
Information

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

Further
Information

References

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	+
1a	B	--
1a	A	+
1a	A	+
1a	A	

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Further
Information

References

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, Gilreath JA et al: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2.2015. 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 $< 100/\mu\text{l} \geq 7\text{d}$**

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

FN risk $\geq 20\%$

FN risk 10-20%

FN risk $< 10\%$

Step 2: Assess factors that may increase the risk of FN:

High risk:

Age > 65 years

Increased risk:

(level I and II evidence)

Advanced disease

History of prior FN

No antibiotic prophylaxis

Other Factors:

(level III and IV evidence)

Poor performance (ECOG > 1)

Female gender

Haemoglobin < 12 g/dL

Liver, renal or cardiovascular disease

Nutritional status

Reassess at each cycle

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk $\geq 20\%$

Overall FN risk $< 20\%$

Prophylactic G-CSF recommended

G-CSF prophylaxis not indicated

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)

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➤ 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.

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 cardiac risk patients**

➤ **Consider alternative regimens
(anthracycline-free, liposomal)**

5 D ++

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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>
www.onkosupport.de

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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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Supportive Therapy

Antiemetics

Wirkstoffgruppe	Substanz	Dosierung	Nebenwirkungen	Potenzial
Serotoninantagonisten	Ondansetron	8 mg i.v., 2 x 4-8 mg p.o., transdermal	Kopfschmerzen, Diarrhoe, Flushsymptomatik Transaminasenanstieg Darmatonie in hoher Dosierung	sehr hoch
	Tropisetron	5 mg i.v., 5 mg p.o.		
	Granisetron	1-3 mg i.v.		
	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) Angstreaktion, Depressionen, Diarrhoe	hoch
	Alizaprid	bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)		
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		
NEPA (Netupitant and Palonosetron)	fixe Kombinationspartner (oral)	NE 300 mg PA 0,5 mg		sehr hoch

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Analgesia

(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie
Tumorschmerz 2014 www.dgs-praxisleitlinien.de)

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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

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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Information

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:

1. 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.
2. Crouch Z, DeSantis ER. :Use of erythropoietin-stimulating agents in breast cancer patients: a risk review. Am J Health Syst Pharm. 2009 Jul 1;66(13):1180-5. Review.PMID: 19535656 [PubMed - indexed for MEDLINE]
3. Hershman DL, Buono DL, Malin J, McBride R, Tsai WY, Neugut AI.:Patterns of use and risks associated with erythropoiesis-stimulating agents among Medicare patients with cancer. J Natl Cancer Inst. 2009 Dec 2;101(23):1633-41. Epub 2009 Nov 10.PMID: 19903808 [PubMed - indexed for MEDLINE]
4. Manzoni M, Delfanti S, Rovati B, Grasso D, Mariucci S, Bencardino K, Tinelli C, Danova M.:Chemotherapy-induced anemia in breast cancer patients treated with pegfilgrastim-supported dose-dense regimens.Clin Exp Med. 2009 Oct 10. [Epub ahead of print]PMID: 19821012 [PubMed - as supplied by publisher]
5. Miller CP, Lowe KA, Valliant-Saunders K, Kaiser JF, Mattern D, Urban N, Henke M, Blau CA.:Evaluating erythropoietin-associated tumor progression using archival tissues from a phase III clinical trial. Stem Cells. 2009 Sep;27(9):2353-61.
6. Crouch Z, DeSantis ER.Use of erythropoietin-stimulating agents in breast cancer patients: a risk review. Am J Health Syst Pharm. 2009 Jul 1;66(13):1180-5.
7. 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:

1. J Oncol Pract. 2010 Nov;6(6):317-20. doi: 10.1200/JOP.2010.000132.
2. 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.
3. Rizzo JD et al: ASCO/ASH/clinical practise guideline/epoetin and darbepoetin/adult patients with cancer. J Clin Oncol 2010; 28: 4996–10
4. 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
5. 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:

1. 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:

1. Rodgers GM und Gilieth JA: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2013 Available from: URL: <http://www.nccn.org>
2. 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 $< 100/\mu\text{l}$ > 7 days) 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

References:

1. Bucaneve G, Micozzi A, Menichetti F, et. al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977-987.
2. Cullen M, Billingham SN, Gaunt C, et. al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-998.
3. Baden LR. Prophylactic antimicrobial agents and the importance of fitness. N Engl J Med 2005;353:1052-1054.
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5. Slavin MA, Lingaratnam S, Mileskin L, Booth DL, Cain MJ, Ritchie DS, Wei A, Thursky KA; Australian Consensus Guidelines 2011 Steering Committee. Use of antibacterial prophylaxis for patients with neutropenia. Australian Consensus Guidelines 2011 Steering Committee. Intern Med J. 2011 Jan;41(1b):102-9.

Relevant Guidelines

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

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment (8/22)

No further information

No references

Relevant guidelines (9/22)

No further information

References

1. 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

Mucositis (10/22)

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 (11/22)

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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Relevant Guidelines:

ASCO:

Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff
2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline J Clin Oncol 24:3187-3205

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 (12/22)

No further information

References:

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2. Smith et al, 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors. J Clin Oncol 24:3187-3205, 2006
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Management of Febrile Neutropenia (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.

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.“

References:

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Relevant Guidelines:

ASCO:

Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff
2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline J Clin Oncol 24:3187-3205

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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 (14/22)

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 (15/22)

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 (16/22)

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

Witte J, de Wit M.

Prävention, Diagnostik und Therapie der zytostatikaassoziierten Paravasation - Was tun wenn's brennt?

Im Focus Onkologie 2010;6:50-55.

Antiemetic Therapy (17/22)

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.

Basch E, Hesketh PJ, Kris MG, Prestrud AA, Temin S, Lyman GH. Antiemetics: american society of clinical oncology clinical practice guideline update. J Oncol Pract. 2011 Nov;7(6):395-8.

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

Schmerztherapie bei Tumorerkrankungen http://www.krebsgesellschaft.de/download/ll_n_02.pdf

Diarrhea (20/22)

No further information

References:

Relevant Guidelines

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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 encouraged 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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4. Candy B, Jones L, Goodman ML, Drake R, Tookman A. Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database of Systematic Reviews* 2011, Issue 1.

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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2. Levy et al, J Natl Compr Canc Netw 10:1284-1309, 2012
3. Cardoso et al, Breast 21:242-252, 2012

Diagnosis And Treatment Of Patients With Primary And Metastatic Breast Cancer

Breast Cancer: Specific Situations

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Breast Cancer: Specific Situations

- **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 ovarian protection 2 weeks prior to CT	1b	B	+/-
➤ Surgery like ≥ 35 y (in particular BCT)	2b	B	+
➤ Stage II–III benefit from PMRT	2b	C	+
➤ Genetic and fertility counseling	2b	B	++

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HEILEN

Breast Cancer During Pregnancy* or Breast Feeding

Oxford / AGO
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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FORSCHEN
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* Participation in register study recommended

Breast Cancer During Pregnancy*

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Oxford / AGO

LoE / GR

➤ Radiation therapy during pregnancy	4	C	-
➤ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
➤ Anthracyclines: AC, EC	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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Information

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* Participation in register study recommended

Breast Cancer During Pregnancy*

Oxford / AGO
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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* Participation in register study recommended

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

- **Clinical geriatric assessment**
- **Treatment according to standard**
 - **Surgery similar to „younger“ age**
 - **Endocrine treatment (endocrine resp.)**
 - **Chemotherapy (standard regimens)**
 - **< 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 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 | B | ++ |
| ➤ Hypofractionated radiotherapy | 2b | C | + |
| ➤ No chemotherapy if >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
- Skin punch biopsy (at least 2; detection rate < 75%)
- Preoperative chemotherapy
 - Regimens as in non-inflammatory BC
 - Anthracycline and taxane-based
 - In HER2 + disease, addition of trastuzumab
 - In HER2 + disease, addition of trastuzumab and pertuzumab
 - In Her2 - addition of bevacizumab
- Mastectomy after chemotherapy
 - Breast conserving therapy in case of pCR
 - Sentinel excision only
- Radiotherapy
- Postoperative systemic therapy as in non-inflammatory BC

		++
2c	B	++
2c	B	+
2c	B	++
2b	B	++
2b	B	++
2b	B	+
2b	C	+/-
2c	B	++
2b	C	+/-
3b	C	--
2c	B	++
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 +
- **Paget's disease with underlying disease (e.g. invasive breast cancer, DCIS)**
 - Therapy according to standard of the underlying disease 5 D ++
 - Surgery must achieve R0 1c B ++
 - Wide excision (like DCIS) + radiotherapy 2b B +
- **Isolated Paget's disease of the NAC:**
 - Surgery must achieve R0 1c B ++
 - Surgical resection only, no adjuvant radiotherapy 4 D ++
 - Sentinel-node excision (SNE) 2b B -

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Malignant and Borderline Phylloides Tumor

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	Oxford / AGO LOE / GR		
➤ Complete (wide) local excision or MRM	2b	B	++
➤ SNE / Axillary dissection in cN0	4	C	--
➤ Staging	5	D	+/-
➤ Systemic adjuvant therapy (chemo, endocrine)	4	C	--
➤ Adjuvant radiotherapy	4	C	--
➤ If T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)	2b	C	+/-
➤ Treatment of local recurrence			
➤ R0 resection	4	C	++
➤ Radiotherapy, chemotherapy after R1 resection	4	C	+/-
➤ Distant metastases (very rare)			
➤ Treatment like soft tissue sarcomas	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 2015 – Solomayer / Harbeck
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 – 2014, ASCO 2005 – 2014, SABCS 2005 – 2014, ECCO/ESMO (2005 – 2014), EBCC (2005 – 2014),
Cochrane data base (2012),
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 \leq 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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International Guidelines:

There is now a bi-annual International Consensus Conference on Breast Cancer in Young women (BCY):

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Benefit from temporary amenorrhoea after adjuvant chemotherapy (chemotherapy induced or GnRHa-related)

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Breast Cancer During Pregnancy or Breast Feeding (5/18)

Further information:

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.

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Statement: Breast imaging & biopsy like in non-pregnant

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3. Nicklas AH et al., Imaging strategies in the pregnant cancer patient. *Semin Oncol* 2000, 27: 623-632
4. Hogge JP et al., Imaging and management of breast masses during pregnancy and lactation. *Breast J* 1999, 5: 272-283.
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6. 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

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

1. Gropper AB¹, Calvillo KZ, Dominici L, Troyan S, Rhei E, Economy KE, Tung NM, Schapira L, Meisel JL, Partridge AH, Mayer EL. Sentinel lymph node biopsy in pregnant women with breast cancer. *Ann Surg Oncol*. 2014 Aug;21(8):2506-11.
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Reviews

1. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
2. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. *Cancer*. 2006 Jan 15;106(2):237-46.
3. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. *Cancer* 1991, 67: 869-872
4. Talele AC, Slanetz PJ, Edmister WB, Yeh ED, Kopa DB. The lactating breast: MRI findings and literature review. *Breast J* 2003, 9: 237-240
5. Scharl A, Ahr A, Göhring U-J: Malignome in der Schwangerschaft. In: Kaufmann M, Costa SD, Scharl A (eds) *Die Gynäkologie*. Springer, Heidelberg, 2002 pp 509
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7. Ben Brahim E, Mrad K, Driss M, Farah F et al. Placental metastasis of breast cancer. *Gynecol Obstet Fertil* 2001, 29: 545-548
8. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5

9. 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

Breast Cancer During Pregnancy (6/18)

No further information

References:

Statement: Radiotherapy during pregnancy

1. Kal HB et al., Radiotherapy during pregnancy: fact and fiction. Lancet Oncol 2005, 6: 328-333 (Review)

Statement: (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant):

1. Loibl S, Han S, Mayer K, MacMillan K, Gyapong S, Luebke K, Weiss C, Schreiber K, Witzel I, Müller V, Schneeweiss A, Mundhenke C, Waldhoer C, Rezek D, Vogt D, Strobel S, Parokonnaya A, Nekljudova V, Amant F, Von Minckwitz G. Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP). J Clin Oncol 32:5s, 2014 (suppl; abstr 1071)
2. Ring et al, Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. J Clin Oncol 2005, 23: 4192-4197
3. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. Ann Oncol. 2008 Apr;19(4):607-13.

Statement: Anthracyclines: AC, EC

4. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46.
5. Peccatori F et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). Breast Cancer Res Treat 2008; Aug 20 [epub ahead of print]
6. Loibl S, Han SN, Amant F. Being Pregnant and Diagnosed with Breast Cancer. Breast Care (Basel). 2012 Jun;7(3):204-209. Epub 2012 Jun 27.

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8. Loibl S et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol.* 2012 13(9):887-96.
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10. Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy: Cignetti F, Bruzzi P, De Placido S, et al. 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. *SABCS 2013: S5-06*

Statement: Taxanes

1. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol.* 2008 Apr;19(4):607-13.
2. Gadducci A, Cosio S, Fanuchi A, Nardini V, Ronce M, Conte PF, Genazzani AR; Chemotherapy with epirubicin and paclitaxel for breast cancer during pregnancy: case report and a review of the literature. *Anticancer Res* 2003; 23: 5225-5
3. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012;13:887-896.
4. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer* 2013;13:16-23.
5. Cardonick E et al. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. *Ann Oncol* 2012;23:3016-3023.

Statement: MTX (e.g. CMF

6. Ring et al., Chemotherapy for breast cancer during pregnancy: An 18-Year experience from five London teaching Hospitals. *J Clin Oncol* 2005, 23: 4192-4197

Statement: Endocrine treatment

7. Cunha GR, Taguchi O, Namikawa R, Nishizuka Y, Robboy SJ Teratogenic effects of clomiphene, tamoxifen, and diethylstilbestrol on the developing human female genital tract *Hum Pathol.* 1987;18:1132–1143.
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9. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381,805–816.

Statement Trastuzumab during pregnancy

10. Fanale MA et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer* 2005, 6: 354-356 (Case Report)
11. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. *Obstetrics and Gynecology* 2005, 105: 642-643 (Case Report)
12. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. *Breast Care* 2008; 3:171-176. (table overview of trastuzumab cases)
13. Aebi S, Loibl S. Breast cancer during pregnancy: medical therapy and prognosis. *Recent Results Cancer Res.* 2008;178:45-55.
14. Clemons M, Goss P: Estrogen and the risk of breast cancer. *New Engl J Med* 2001, 344: 276-285
15. Azim HA Jr et al. Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). *Breast Cancer Res Treat.* 2012;133(1):387-91.
16. Zagouri F et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013 Jan;137(2):349-57.
17. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* 2013; 5(7):733-41.

Statement Bisphosphonate during pregnancy

18. Levy S, Favez I, Taguchi N, Han JY, Aiello J, Matsui D, Moretti M, Koren G, Ito S. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone*. 2009 Mar;44(3):428-30.
19. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet*. 2012 Feb 11;379(9815):570-9. Review.

General information: Chemotherapy during pregnancy

1. Murthy RK, Theriault RL, Barnett CM, Hodge S, Ramirez MM, Milbourne A, Rimes SA, Hortobagyi GN, Valero V, Litton JK. Outcomes of children exposed in utero to chemotherapy for breast cancer. *Breast Cancer Res*. 2014 Dec 30;16(6):3414.

Breast cancer during pregnancy (7/18)

Further information:

These statements are derived from common sense and literature cannot fully be assigned.

References:

In general

1. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012 Feb 11;379(9815):570-9.
2. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-896.
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

6. Williams Obstetrics lecture book
7. Pistilli B et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: how should we counsel cancer patients about breastfeeding? Cancer Treat Rev. 2013;39(3):207-11.

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.

References:

Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately

1. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy associated breast cancer. Cancer 1991, 67: 869-872
2. Loibl S, von Minckwitz G, et al., Breast carcinoma during pregnancy. Cancer. 2006 Jan 15;106(2):237-46
3. Rodriguez et al. Evidence of poorer survival in pregnancy-associated breast cancer. Obstet Gynecol. 2008 Jul;112(1):71-8
4. Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 2009;27:45-51. doi:10.1200/JCO.2008.17.4110.
5. Kranick JA, Schaefer C, Rowell S, Desai M, Petrek JA, Hiatt RA, Senie RT. Is pregnancy after breast cancer safe? Breast J. 2010 Jul-Aug;16(4):404-11.
6. Azim HA Jr., Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. Cancer Treat Rev 2012;38:834-842.
7. Amant F et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study J Clin Oncol. 2013;31(20):2532-9.

8. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist*. 2013;18(4):369-76.

Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

9. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. *JCO* 2001; 19: 1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).
10. Kroman N et al. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol*. 2008;47(4):545-9
11. Azim HA Jr et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol* 2013;31:73-79.

Review articles

1. Del Mastro et al, Infertility and pregnancy after breast cancer: current knowledge and future perspectives. *Cancer Treat Rev*. 2006 Oct;32(6):417-22. Epub 2006 Jul 13. Review.
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.
3. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer*. 2011 Jan;47(1):74-83. Epub 2010 Oct 11. Review.
4. Pagani O, Azim H Jr. Pregnancy after Breast Cancer: Myths and Facts. *Breast Care (Basel)*. 2012 Jun;7(3):210-214. Epub 2012 Jun 27.
5. Valachis A, Tsali L, Pesce LL, Polyzos NP, Dimitriadis C, Tsalis K, Mauri D Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv*. 2010 Dec;65(12):786-93.

8. Azim HA Jr, Santoro L, Russell-Edu W, Pentheroudakis G, Pavlidis N, Peccatori FA. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev.* 2012 Nov;38(7):834-42. Epub 2012 Jul 9. Review.
9. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet.* 2012 Feb 11;379(9815):570-9.
10. 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

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,

References:

1. Biganzoli L 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 13 (4):e 148-e160
2. Charlson et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-383.
3. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006 295:801-08.
4. Wildes TM et al. Geriatric assessment is associated with completion of chemotherapy, toxicity, and survival in older adults with cancer. J Geriatr Oncol. 2013;4(3):227-34.
5. Aaldriks AA. Prognostic value of geriatric assessment in older patients with advanced breast cancer receiving chemotherapy et al. Breast 2013;22(5):753-60.
6. Bellera CA et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012;23(8):2166-72

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%, $p=0.836$).

References:

Statement: Treatment according to standard

1. Bouchardy C et al., Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol. 2003;21(19):3580-7
2. Enger SM: Breast cancer treatment of older women in integrated health care settings. J Clin Oncol. 2006 Sep 20;24(27):4377-83
3. Mustacchi G, Breast cancer in elderly women: a different reality? Results from the NORA study. Ann Oncol. 2007 Jun;18(6):991-6.

4. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. Am J Surg. 2006 Sep;192(3):317-21
5. Kemeny MM: Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003 Jun 15;21(12):2268-75
6. Giordano SH: Breast cancer treatment guidelines in older women. J Clin Oncol. 2005 Feb 1;23(4):783-91.
7. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. J Am Coll Surg. 2008 Jan;206(1):66-75
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
9. Luque M et al. Breast cancer management in the elderly. Clin Transl Oncol. 2013 epub

Statement: Surgery similar to „younger“ age

1. Swaminathan V. et al. Choices in Surgery for older women with breast cancer Breast Care 2012;7:445-451
2. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. Eur J Cancer. 2003 Feb;39(3):309-16
3. Fentiman IS: Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10850 comparing modified radical mastectomy with tumorectomy plus tamoxifen. Eur J Cancer. 2003 Feb;39(3):300-8
4. Hind D: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br J Cancer 2007 Apr 10;96(7):1025-9.
5. Rudenstam CM Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol. 2006 Jan 20;24(3):337-44.
6. Martelli G, Miceli R, Daidone MG, Vetrella G, Cerrotta AM, Piromalli D, Agresti R. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol. 2011;18(1):125-33
7. Johnston SJ et al. A randomised trial of primary tamoxifen versus mastectomy plus adjuvant tamoxifen in fit elderly women with invasive breast carcinoma of high oestrogen receptor content: long-term results at 20 years of follow-up. Ann Oncol 2012;9:2296-300.

8. Chakrabarti J et al. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up.Crit Rev Oncol Hematol. 2011;78(3):260-4.

Statement: Endocrine treatment (endocrine resp.)

10. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 Trial. J Clin Oncol 2008; 26:1972-79
11. Muss H et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol. 2008 Apr 20;26(12):1956-64
12. Lash TL: Physicians' assessments of adjuvant tamoxifen's effectiveness in older patients with primary breast cancer.J Am Geriatr Soc. 2005 Nov;53(11):1889-96
13. Silliman RA: Adjuvant tamoxifen prescription in women 65 years and older with primary breast cancer.J Clin Oncol. 2002 Jun 1;20(11):2680-8
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15. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381, 805–816

Statement: Chemotherapy in pts. < 70 years

16. Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. Breast Cancer Res. 2008 Sep16;10(5):R77
17. Fisher B: Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: updated findings from National Surgical Adjuvant Breast and Bowel Project clinical trials.J Natl Cancer Inst. 2004 Dec 15;96(24):1823-31.

18. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial. *J Clin Oncol*. 2004 Dec 1;22(23):4622-30
19. Du XL: Effectiveness of adjuvant chemotherapy for node-positive operable breast cancer in older women. *J Gerontol A Biol Sci Med Sci*. 2005 Sep;60(9):1137-44
20. De Maio E et al., Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: a single-center experience. *BMC Cancer* 2005 24: 30
Muss HB et al., Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA* 2005, 293:1073-81.
21. Chagpar AB: Determinants of early distant metastatic disease in elderly patients with breast cancer. *Am J Surg*. 2006 Sep;192(3):317-21.
22. Hurria A et al., Patterns of toxicity in older patients with breast cancer receiving adjuvant chemotherapy. *Breast Cancer Res Treat*. 2005 92:151-6.
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Statement: Chemotherapy in pts. > 70 years:

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2. Loibl S. et al Present Status of Adjuvant Chemotherapy for Elderly Breast Cancer Patients *Breast Care* 2012;7:439-444
3. Muss HB, Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med*. 2009 May 14;360(20):2055-65.
4. Muss HB: CLGB: Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol*. 2007 Aug 20;25(24):3699-704
5. Muss HB: Adjuvant treatment of elderly breast cancer patients. *Breast*. 2007 Nov;16 Suppl 2:159-65

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7. Crivellari D et al. Adjuvant pegylated liposomal doxorubicin for older women with endocrine nonresponsive breast cancer who are NOT suitable for a "standard chemotherapy regimen": the CASA randomized trial. *Breast*. 2013;22(2):130-7.

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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25. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control *Strahlenther Onkol* 2012 :1-5
26. Giordano SH Radiotherapy in older women with low-risk breast cancer: why did practice not change? 2012 *J Clin Oncol* 30 (14): 1577-1578
27. Prescott RJ: A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess*. 2007 Aug;11(31):1-149, iii-iv
28. Yood MU: Mortality impact of less-than-standard therapy in older breast cancer patients. *J Am Coll Surg*. 2008 Jan;206(1):66-75
29. Hughes KS 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(19):2382-7

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Statement: Trastuzumab

1. Freedman RA, Vaz-Luis I, Barry WT, Lii H, Lin NU, Winer EP, Keating NL. Patterns of chemotherapy, toxicity, and short-term outcomes for older women receiving adjuvant trastuzumab-based therapy. *Breast Cancer Res Treat.* 2014 Jun;145(2):491-501.
2. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, Smith BD, Hortobagyi GN, Giordano SH. Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol.* 2013 Nov 20;31(33):4222-8
3. Guarneri V: Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol.* 2006 Sep 1;24(25):4107-15.
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5. 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 Jan 6;369(9555):29-36
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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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4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).
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Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):

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Statement: No axillary clearing (≥ 60 y, cN0, Rec pos)

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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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International registry:

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Statement: Diagnostic work up as in women

Statement: Mammography

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Statement: Ultrasound

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Statement: Standard-surgery: Mastectomy –men

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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)

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Statement: Screening for 2nd malignancies according guidelines

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Statement: Systemic therapy

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28. Patten DK et al. New Approaches in the Management of Male Breast. *Cancer Clinical Breast Cancer* 2013;13(5) 309–314
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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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Statement Trastuzumab

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Statement endocrine therapy

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Statement palliative chemotherapy

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Primary Inflammatory Breast Cancer (IBC; 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

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Statement: Regimens as in non-inflammatory BC

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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: in HER2 positive disease addition of trastuzumab and pertuzumab

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Statement: in HER2 negative disease addition of bevacizumab

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Statement: Mastectomy after chemotherapy

1. 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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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

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Statement: Postoperative systemic therapy as in non-inflammatory BC

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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:

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Statement: Mammography / Breast ultrasound/ Breast MRI

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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:

Pagest'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

Review:

1. Toodayan N. The Paget bicentenary: An Australian perspective. J Med Biogr pii0967772014533055

Malignant and Borderline 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: Core biopsy

1. Hyun Kyung Jung, Hee Jung Moon, Min Jung Kim, Eun-Kyung Kim Benign core biopsy of probably benign breast lesions 2 cm or larger: correlation with excisional biopsy and long-term follow-up. *Ultrasonography* 2014;33:200-205
2. Abdulkadir D, Nori J, Meattini I, Giannotti E, Boeri C, Vanzi E, Vezzosi V, Bianchi S. Phyllodes tumours of the breast diagnosed as B3 category on image-guided 14-gauge core biopsy: analysis of 51 cases from a single institution and review of the literature. *Eur J Surg Oncol.* 2014 Jul;40(7):859-64. doi: 10.1016/j.ejso.2014.02.222. Epub 2014 Feb 21

Statement: Diagnosis

1. Kamitani T, Matsuo Y, Yabuuchi H, Fujita N, Nagao M, Kawanami S, Yonezawa M, Yamasaki Y, Tokunaga E, Kubo M, Yamamoto H, Honda H. Differentiation between benign phyllodes tumors and fibroadenomas of the breast on MR imaging. *Eur J Radiol.* 2014 Aug;83(8):1344-9. doi: 10.1016/j.ejrad.2014.04.031. Epub 2014 May 9.

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

1. 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
2. Shingo Baba¹, Takuro Isoda, Yasuhiro Maruoka, Yoshiyuki Kitamura, Masayuki Sasaki, Tsuyoshi Yoshida, and Hiroshi Honda Diagnostic and Prognostic Value of Pretreatment SUV in 18F-FDG/PET in Breast Cancer: Comparison with Apparent Diffusion Coefficient from Diffusion-Weighted MR Imaging. J Nucl Med 2014; 55:736–742

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)

1. Pezner et al Malig. Phy. Tu. Of the breast: local control rates with surgery alone (2008): Int. J Radiat. Oncol. Biol. Phys
2. Jerzy Mitus, Marian Reinfuss, Jerzy W. Mitus, Jerzy Jakubowicz, Pawel Blecharz, Wojciech M. Wysocki and Piotr Skotnicki. Malignant Phyllodes Tumor of the Breast: Treatment. and Prognosis. The Breast Journal, Volume 20 Number 6, 2014 639–644
3. Jennifer L. Gnerlich, MD, Richelle T. Williams, MD, Katherine Yao, MD, Nora Jaskowiak, MD,
4. and Swati A. Kulkarni, MD. Utilization of Radiotherapy for Malignant Phyllodes Tumors: Analysis of the National Cancer Data Base, 1998–2009. Ann Surg Oncol (2014) 21:1222–1230

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).
3. Jerzy Mitus, Marian Reinfuss, Jerzy W. Mitus, Jerzy Jakubowicz, Pawel Blecharz, Wojciech M. Wysocki and Piotr Skotnicki. Malignant Phyllodes Tumor of the Breast: Treatment. and Prognosis. The Breast Journal, Volume 20 Number 6, 2014 639–644

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.
2. Wang H, Wang X, Wang CF Comparison of clinical characteristics between benign borderline and malignant phyllodes tumors of the breast. *Asian Pac J Cancer Prev*. 2014;15(24):10791-5.

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

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Scharl / Solomayer / Thomssen**
- **Version 2015:**
Maass / Rody

Breast Cancer Follow-Up Objectives I

Oxford / AGO

LoE / GR

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 -

* loco-regional recurrence is associated with higher risk for mortality in node positive, PR negative, younger patients and patients with short time from diagnosis to recurrence

Breast Cancer Follow-Up Objectives II

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**Oxford / AGO
LoE / GR**

- **Improve quality of life**
- **Improve physical performance**
- **Reduce therapy related side effects
as osteoporosis, cardiac failure, fatigue,
neurotoxicity, lymphedema**

2b B +

2b B +

2b B +

Breast Cancer Follow-Up Objectives III

Oxford / AGO

LoE / GR

- **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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Breast Cancer Follow-Up Objectives

Oxford / AGO

LoE / GR

➤ 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, prophylactic surgery, breast reconstruction)

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

Oxford / AGO

LoE / GR

- **Treatment of type II-diabetes** ++
(>25% undetected DM in postmenopausal BC patients)
- **Weight intervention** 2a B +
(if BMI <18.5 and >40)
- **Reduction of dietary intake (at least 15 % calories from fat)** 2b B +
in HR neg. breast cancer patients is
associated with improved overall survival
- **Smoking** 2b B ++
(bc related mortality 2 x and BC unrelated mortality 4 x elevated)
- **Reduce alcohol consumption below 6 g/d** 2b B +
- **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

**Oxford / AGO
LoE / GR**

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	-

Early Detection of Potentially Curable Events

Oxford / AGO
LoE / GR

Local recurrence & in-breast recurrence:

- Incidence 7–20%
(depending on time of F/U)
- Breast self-examination 5 D +
- Physical examination, mammography & US 1a B ++
- Magnetic resonance imaging (MRI) 3b B +/-

Further
Information

References

Early Detection of Potentially Curable Events

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LoE / GR

Contralateral breast cancer:

- Rel. risk: 2,5–5
- Incidence: 0,5–1,0 % / year
- **Breast self-examination**

5	D	+
----------	----------	----------
- **Physical examination, mammography & US**

1a	A	++
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- **Routine breast MRI**

5	D	-
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Early Detection of Potentially Curable Events

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LoE / GR**

Unrelated site carcinoma:

- Colon RR 3,0; endometrium RR 1,6
ovary RR ca. 1,5; lymphoma RR7
- 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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Further Information

References

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 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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HEILEN

Breast Cancer Follow-up Duration. Breast Nurses.

**Oxford / AGO
LoE / GR**

➤ Duration of follow-up

➤ until 5 yrs

1c A ++

➤ until 10 yrs

1c A +

➤ Surveillance by specialized 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.**

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Further
Information

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Breast Cancer Follow-Up (2/17)

No further information

No references

Breast Cancer Follow-Up, Objectives I (3/17)

No further information

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Statement: Psycho-social aspects

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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 II (4/17)

No further information

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Statement: Obesity and breast cancer prognosis

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Statement: lymphedema

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Breast Cancer Follow-Up, Objectives III (5/17)

No further information

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Statement: Re-evaluation of current adjuvant therapy

1. Expert opinion Organkommission

Statement: Monitoring of compliance

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Breast Cancer Follow-Up, Objectives (6/17)

No further information

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Statement: Psycho-social aspects

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Statement: prophylactic surgery

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Breast Cancer Follow-Up, Objectives (7/17)

No further information

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Statement: Early Detection

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Follow-up Objectives - Reported by Patients (8/17)

No further information

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Follow-up Goals Reported by Health Professionals and Patients (9/17)

No further information

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Routine Follow-Up Examinations in Asymptomatic Patients (10/17)

No further information

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.
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Statement: Physical examination

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Statement: Breast self-examination

Expert Opinion

Statement: Mammography

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Statement: MRI of the breast in case of inconclusive conventional imaging

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Statement: Pelvic examination

Expert Opinion

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Routine Follow-Up Examinations in Asymptomatic Patients (11/17)

No further information

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.
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Statement: Routine biochemistry (incl. tumor markers)

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Statement: Ultrasound of the liver

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Statement: Bone scan

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Statement: Chest X-ray

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Statement: CT of chest, abdomen and pelvis

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Statement: Detection of isolated/circulating tumor cells

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Statement: PET

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Early Detection of Potentially Curable Events (12/17)

No further information

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Statement physical examination, mammography & US

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Breast Cancer Follow-up - Duration. Breast Nurses. (16/17)

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Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients (17/17)

No further information

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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 2003–2014:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Lisboa / Maass /
Mundhenke / Rezai / Solomayer /
Souchon / Thomssen**
- **Version 2015:**
Fersis / Harbeck

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	3b	B	++
➤ Complete re-staging	5	D	++

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Risk Factors for Loco-Regional Recurrence 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 |
| ➤ Obesity (Body mass index) | 1a |

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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

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Information

References

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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

2a B

2a B

2b B

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.)

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 AxDiss 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 -

1b B +/-

5 D +

*If no sentinel lymph node can identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended

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Information

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Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

**Oxford AGO
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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** **+**

Chemotherapie bei lokoregionärem Rezidiv

➤ CALOR Trial

n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection

5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy vs. 57% (44-67) without chemotherapy (hazard ratio 0.59 [95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).

Adjuvant chemotherapy was significantly more effective in ER negative disease (p_{interaction}=0.046).

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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 (with chemotherapy) 5 D ++

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References

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 - 2015, ASCO 2005 – 2015, SABCS 2009 – 2014, Cochrane data base

Guidelines:

Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordström EB, Pagni O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014 Oct;23(5):489-502.

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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 an 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.

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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.

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Statement: Increased risk for loco-regional recurrence

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Statement: Young age

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Statement: Positive microscopic margins

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Statement: Extensive intraductal component

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Statement: Vessel invasion

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Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors

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Statement: Grading (G3 vs. G1)

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Statement: pT (> 2 vs. ≤ 2cm)

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Statement: pT (> 2 vs. ≤ 2cm) and Grading (G3 vs. G1) in node negative

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Statement: pN (N1 vs. N0)

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Statement: number of involved lymph nodes

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Statement: Medial tumor localisation (vs. central/lateral)

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Statement: elevate proliferation marker, esp. Ki67

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Statement: Inflammatory breast cancer

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Statement: Nomograms

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Statement: Obesity

1. D. S. M. Chan et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914. Published online Apr 27, 2014.
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Recent evidence for Multigene arrays predicting risk for local relapse:

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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
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Statement: Multifocality

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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
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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

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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 analyses 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. 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 \pm 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, Tartter 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
6. Maaskant-Braat AJ¹, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat.* 2013 Feb;138(1):13-20. doi: 10.1007/s10549-013-2409-1. Epub 2013 Jan 23
7. Kothari MS¹, Rusby JE, Agusti AA, MacNeill FA.: Sentinel lymph node biopsy after previous axillary surgery: A review. *Eur J Surg Oncol.* 2012 Jan;38(1):8-15. doi: 10.1016/j.ejso.2011.10.003. Epub 2011 Oct 26.
8. Uth CC¹, Christensen MH, Oldenbourg MH, Kjær C, Garne JP, Teilum D, Kroman N, Tvedskov TF. Sentinel Lymph Node Dissection in Locally Recurrent Breast Cancer. *Ann Surg Oncol.* 2015 Jan 7. [Epub ahead of print]

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 - Surgery (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 (re-adjuvant) 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. Aebi S, Gelber S, Anderson SJ, Láng I, Robidoux A, Martín M, Nortier JW, Paterson AH, Rimawi MF, Cañada JM, Thürlimann B, Murray E, Mamounas EP, Geyer CE Jr, Price KN, Coates AS, Gelber RD, Rastogi P, Wolmark N, Wapnir IL; **CALOR** investigators. Chemotherapy for isolated locoregional recurrence of breast cancer (**CALOR**): a randomised trial. Lancet Oncol. 2014 Feb;15(2):156-63.

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.
4. 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 Radiation Oncology Biol Phys* 72: 1456-64, 2008.

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
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 (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.
3. Easson AM, McCready DR: Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004

4. 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.
5. 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 Radiation Oncology Biol Phys 72: 1456-64, 2008
6. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17Version 3.2012
7. 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. It needs to be emphasized that in some of the registration studies such as CLEOPATRA locally advanced, not operable tumors had been included.

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
3. 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
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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5. 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: 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, Dewhurst 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
9. Kouloulis VE, Dardoufas CE, Kouvaris JR, Gennatas CS, Polyzos AK, Gogas HJ, Sandilos PH, Uzunoglu NK, Malas EG, Vlahos LJ. Liposomal doxorubicin in conjunction with reirradiation and local hyperthermia treatment in recurrent breast cancer: a phase I/II trial. Clin Cancer Res 8(2):374-82,2002
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
3. Sersa G, Cufer T, Paulin SM, Cemazar M, Snoj M. Cancer Treat Rev. Electrochemotherapy of chest wall breast cancer recurrence 38(5):379-86, 2012

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Version 2015.1

Endocrine and “Targeted” Therapy in Metastatic Breast Cancer

Endocrine Therapy of Metastatic Breast Cancer

➤ **Version 2002:**

Gerber / Friedrichs

➤ **Versions 2003–2014:**

**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat / Kaufmann /
Loibl / Lück / von Minckwitz / Müller /
Mundhenke / Nitz / Schneeweiß / Schütz /
Stickeler**

➤ **Version 2015:**

Liedtke / Möbus

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/PR and HER2 Metastasis vs. Primary Tumor

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Metaanalysis based on 48 (mostly retrospective) analyses:

Pooled discordance proportions were

- 20% (95%CI 16-35%) for ER
- 33% (95%CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Pooled proportions of tumours shifting from positive to negative and negative to positive were

- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2

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Further
Information

References

Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer

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	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	--

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Further
Information

References

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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 + AI (vs. AI)
- Letrozol + Palbociclib (vs. Letrozol)

Oxford / AGO
LoE / GR

1a	A	++
1a	A	++
1b	B	++
2b	B	+
1a	A	+/-
1b	B	+/-
2b	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 Patients with HER2 Negative Metastatic Breast Cancer

(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	++
	aromatase inhibitor**	2b	B	+
	tamoxifen + everolimus	2b	B	+
Further	tamoxifen	3b	C	+
lines:	MPA/MA	4	D	+/-
	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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sowie
in der DKG e.V.

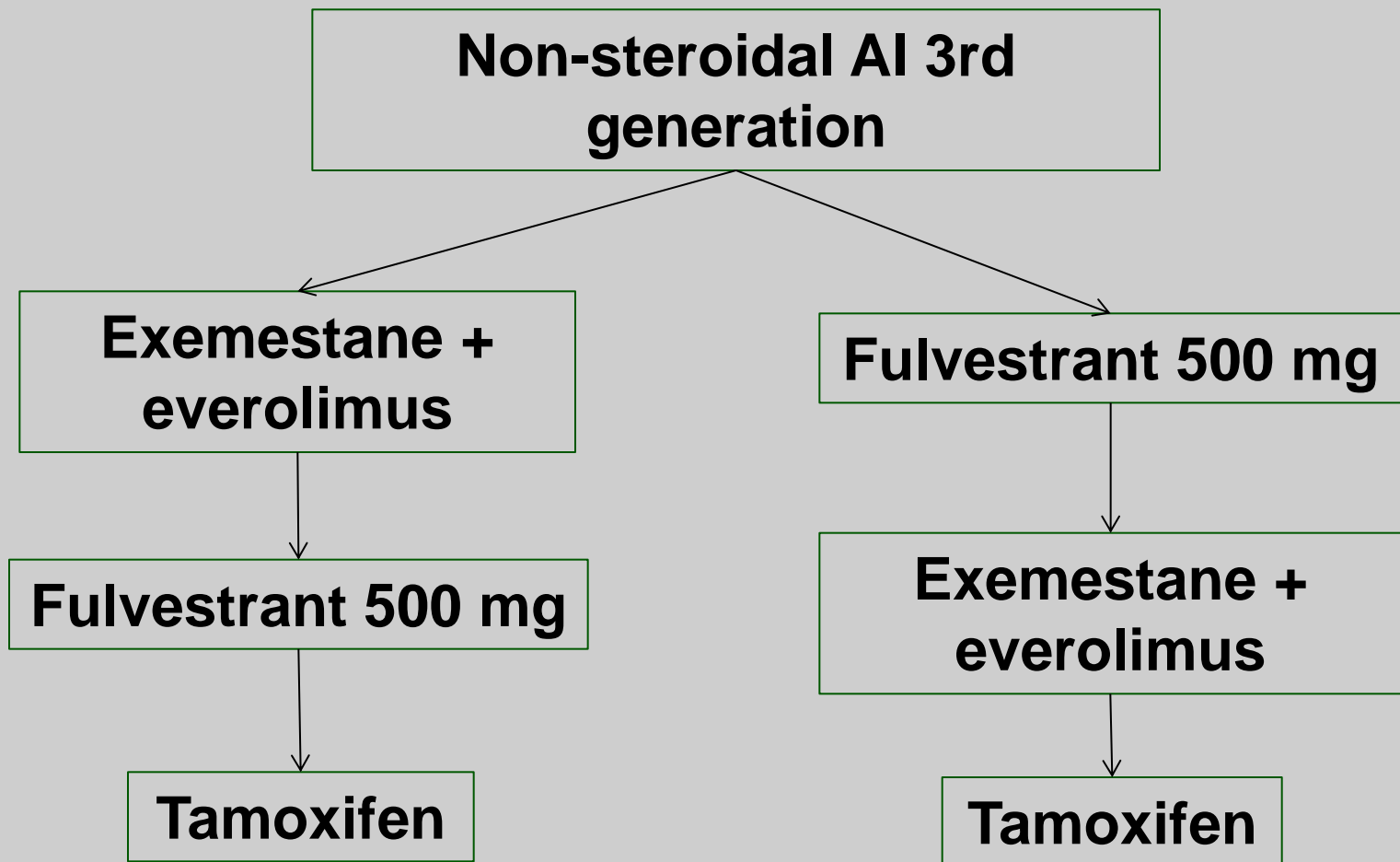
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Further
Information

References

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Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer after Adjuvant AI

Treatment sequence

Oxford / AGO
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

Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab

Oxford / AGO
LoE / GR

- **Maintenance Bevacizumab plus endocrine therapy after remission with chemotherapy and Bevacizumab**
- **Bevacizumab plus endocrine treatment as first line therapy for advanced disease**

2b^a B +

1b^a B -

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Information

References

**FORSCHEN
LEHREN
HEILEN**

Therapy Algorithm After Adjuvant AI

**Short treatment free
interval ≤ 12 months**

**Exemestane +
everolimus**

Fulvestrant 500 mg

Tamoxifen

**Long treatment free
interval > 12 months**

Fulvestrant 500 mg

Tamoxifen

**Exemestane +
everolimus**

Tamoxifen

Fulvestrant 500 mg

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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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	-

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**Poor efficacy of endocrine therapy alone.
Consider chemotherapy + anti-HER2-therapy!**

Combination of Endocrine Treatment with Anti-HER2-Treatment

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)	14,1 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)	4.1 vs. 3.8 (HER2-) 5.9 vs. 3.3 (HER2+)	38 vs. 17%	30 vs. 26.4 mo (all)

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LEHREN
HEILEN

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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References

FORSCHEN
LEHREN
HEILEN

Endocrine Therapy of Metastatic Breast Cancer (2/15)

Further information:

Screened data bases Pubmed, ASCO, San Antonio, EBCC, ESMO

No references

Endocrine Therapy in Metastatic Breast Cancer – Indication (3/15)

Further information and references:

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 menopausal status of the patient, the type of adjuvant endocrine therapy received, and past medical history of thrombotic disease. HER-2-positive metastatic breast cancer is less responsive to any type of endocrine treatment. This effect holds in the subgroup of patients with positive or unknown steroid receptors

Response to endocrine therapy by hormone receptor status

A Cochrane Data Base Meta-Analysis was performed in 2003 on 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.

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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 with divergent results.

A recently 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.

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). 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 2009).

Additionally there is further 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).

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Comparison ER/PgR and HER2 Metastasis vs. Primary Tumor (4/15)

Further information:

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 with divergent results.

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Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer (5/15)

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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GnRHa + AI

Even if the evidence is rather limited, aromatase inhibitors can be an option in the treatment of metastatic premenopausal breast cancer.

Majorly based on a Phase II trial by Forward et al. 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). However, since this study is very small, additional body of evidence is needed before general treatment recommendations can be made. Recently 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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GnRH plus Fulvestrant

GnRH analogues can be combined with fulvestrant. This combination can be an alternative approach in selected cases e.g. if there is a contraindication for tamoxifen or ARH.

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Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer (6/15)

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 major treatment option in the metastatic setting despite the superiority of aromatase inhibitors for first line treatment.

Fulvestrant in the approved dose of 250mg every four weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of MBC.

Despite convincing preclinical data supporting the combined therapy strategy of fulvestrant plus an aromatase inhibitors, there is overall conflicting evidence regarding efficacy in patients. While evidence from two prospective clinical trials (i.e. FACT and SoFEA) did not demonstrate any advantage by adding fulvestrant to anastrozole another trial showed that the combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant. Therefore, combined use of these agents cannot be recommended.

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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Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no prior Endocrine Treatment (7/15)

Further information:

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 therefore seems as likely that a switch from steroidal to non steroidal AI is effective and may therefore represent a therapeutic option.

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.

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Fulvestrant and anastrozole

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Exemestane and everolimus

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Therapy Algorithm After Adjuvant Tamoxifen (8/15)

No further information

No references

Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant AI (9/15)

Further information:

For patients with progression or relapse after a short treatment free interval after the adjuvant use of an AI (in studies usually considered as one year or less), the same considerations as for second line treatment after AI use should be applied. In a randomised Phase-II-study the addition of palbociclib to letrozole significantly improved progression-free survival in women with advanced oestrogen receptor-positive and HER2-negative breast cancer. A phase 3 trial is currently underway.

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Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients in combination with Bevacizumab (10/15)

Further information:

For patients with HR-positive advanced breast cancer on first-line therapy with bevacizumab in combination with chemotherapy who discontinue chemotherapy without evidence of progression, continuation of bevacizumab therapy in combination with endocrine therapy is recommended until disease progression or toxicity.

In the LEA study adding bevacizumab to first-line endocrine therapy with letrozole or fulvestrant failed to demonstrate significant increases in progression-free survival in postmenopausal women with advanced human epidermal growth-factor receptor 2 (HER2)-negative and hormone-receptor-positive (HR+) breast cancer.

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Therapy Algorithm After Adjuvant AI (11/15)

No further information

No references

Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients (13/15)

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 3 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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Combination of Endocrine Treatment with Anti-HER2-Treatment (14/15)

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 3 trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients.

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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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Concomitant or Sequential Endocrine-Cytostatic Treatment (15/15)

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 maintenance 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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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

 START

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***Substances are only discussed if there is at least published evidence
based 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 2003–2014:**
**Bischoff / Dall / Fersis / Friedrichs / Harbeck /
Jackisch / Janni / Möbus / Rody / Scharl /
Schmutzler / Schneeweiss / Schütz / Stickeler
/Thomssen**

- **Version 2015:**
von Minckwitz / Müller

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Further
Information

References

Disease-Free and Overall Survival in Metastatic Breast Cancer

Oxford / AGO
LoE / GR

- An increase in survival over time in MBC has been shown in some retrospective analyses 2a
- However, patients with MBC today have received more adjuvant treatment and have therefore considered more drug resistant 2a
- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity) 1b
- Especially targeted drugs in combination with chemotherapy can induce substantial survival benefits 1b

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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	++
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 patients of older age, with reduced performance status, or significant co-morbidities)**
- **Assess subjective and objective toxicities, symptoms, and performance status 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 slowly growing disease, longer intervals are acceptable.**

Cytotoxic Therapy Duration

**Oxford / AGO
LoE GR**

As long as therapeutic index remains positive

1a A ++

- **Treatment until progression**
- **Treatment until best response**
- **Change to alternative regimen
before progression**

2b B +

2b B +/-

2b B +/-

- **Stop therapy in case of**

1c A ++

- **Progression**
- **Non tolerable toxicity**

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)**
- **Disease-free interval after end of adjuvant treatment**
- **Aggressiveness of disease and localization of metastases**
- **Estimated life expectancy**
- **Co-morbidities (including organ dysfunctions)**
- **Patients preference and expectations**

MBC HER2-negative/HR-positive Cytotoxic 1st-Line Therapy*

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Monotherapy:

- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, mitoxantrone (A)
Peg. liposomal doxorubicin (A_{lip})
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

Oxford / AGO LoE / GR

1b	A	++
1b	A	++
3b	B	+
2b	B	+
2b	B	+

Polychemotherapy:

- A + T
- T + gemcitabine after adj. A
- A + C or A_{lip} + C
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A

1b	A	++
2b	B	++
1b	B	++
2b ^a	B	+
1b	A	+

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*In ER pos. disease only if endocrine therapy is not or not anymore indicated

MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

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- Paclitaxel q1w
- Docetaxel q3w
- Capecitabine
- Nab-paclitaxel
- Peg-liposomal doxorubicin
- Eribulin
- Vinorelbine
- Docetaxel + Peg-liposomal Doxo

Oxford / AGO
LoE / GR

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

*independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant 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	-

***Cave neutropenia / therapeutic index!**

Triple Negative Metastatic Breast Cancer

**Oxford / AGO
LoE / GR**

- **Experimental therapies within studies**
- **Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC**
- **Carboplatin (vs. Docetaxel)**
 - **in gBRCA mutation**
- **Gemcitabine/Cisplatin (vs. GemPac)**
- **Bevacizumab added to first line cytotoxic therapy**

++

+

1b^a B +/-

1b^a B +

1b^a A +

2b B +

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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)

➤ Cap+Bev as maintenance after Doc+Bev

➤ 2nd line as treatment through multiple lines

➤ 2nd line in combination with:

- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

Oxford / AGO
LoE / GR

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

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

	Oxford / AGO LoE / GR		
➤ Docetaxel + trastuzumab + pertuzumab	1b	A	++
➤ (nab)Paclitaxel + trastuzumab + pertuzumab	2b	B	+
➤ 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	-
➤ Taxanes + trastuzumab + everolimus	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

2nd line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)

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Oxford / AGO
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➤ T-DM 1	1b	A	++
➤ TBP: 2 nd line chemotherapy + trastuzumab	2b	D	+
➤ Capecitabine + lapatinib	1b	B	+
➤ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+
➤ Taxane + trastuzumab + pertuzumab	5	D	+
➤ Any other 2 nd line chemotherapy* + trastuzumab + pertuzumab	5	D	+/-
➤ Trastuzumab + aromatase inhibitors (if ER+)	3b	B	+
➤ Lapatinib + aromatase inhibitors (if ER+)	3b	B	+

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

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

Oxford / AGO
LoE / GR

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.

Lapatinib in HER2-positive Metastatic Breast Cancer

Oxford / AGO
LoE / GR

In combination with

- Trastuzumab for heavily pre-treated pts
- Paclitaxel in 1st line
- Capecitabine in > 2nd line
- AI in ER positive disease

2b B +

2b B -

1b B +

2b B +/-

- In patients with brain metastases (radioresistance) in combination with capecitabine

2b B +/-

Immunodiagnostic Tests and Immunotherapy

Oxford / AGO
LoE / GR

Immunodiagnostic tests:
Immunological parameters in peripheral blood

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**
- **Checkpoint inhibitors (PD1; PDL-1;...)**

Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/18)

Further information and references:

International consensus

Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordstrom EB, Pagani O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol. 2014;25:1871-88.

Update since 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).

Disease-Free and Overall Survival in Metastatic Breast Cancer (3/18)

No further information

References:

Increase

1. Petrelli F, Barni S. Surrogate endpoints in metastatic breast cancer treated with targeted therapies: an analysis of the first-line phase III trials. Med Oncol. 2014;31:776.

More adjuvant..

Multiple lines

1. 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. 2013;22:314-9.

Treatment of Metastatic Breast Cancer - Predictive Factors (4/18)

No further information

References:

CTC monitoring

1. Bidard FC, Peeters DJ, Fehm T, Nole F, Gisbert-Criado R, Mavroudis D, Grisanti S, Generali D, Garcia-Saenz JA, Stebbing J, Caldas C, Gazzaniga P, Manso L, Zamarchi R, de Lascoiti AF, De Mattos-Arruda L, Ignatiadis M, Lebofsky R, van Laere SJ, Meier-Stiegen F, Sandri MT, Vidal-Martinez J, Politaki E, Consoli F, Bottini A, Diaz-Rubio E, Krell J, Dawson SJ, Raimondi C, Rutten A, Janni W, Munzone E, Caranana V, Agelaki S, Almici C, Dirix L, Solomayer EF, Zorzino L, Johannes H, Reis-Filho JS, Pantel K, Pierga JY, Michiels S. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol.* 2014;15:406-14.

(Hilner et al. 2003 JCO)

Cytotoxic Therapy Goals (5/18)

Further information and references:

(O'Shaughnessy *et al*, 2003, Albain, 2004)

(Sledge *et al*, 2003).

(S Carrick *et al*, The Cochrane Database of Systematic Reviews 2005)

2013

Combination vs single agent

1. 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
2. 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.

1. 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.

1. 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.

1. 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.

Cytotoxic and Targeted Therapy (6/18)

No further information

References:

1. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordstrom EB, Pagani O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)dagger. Ann Oncol. 2014;25:1871-88.

Cytotoxic Therapy Duration (7/18)

Further information:

Consent

Treatment until progression 6++, 18+, 2+/-, 1-

Treatment until best response 1++, 3+, 23+/-, 1-

Change to alternative regimen before progression 1++, 0+, 25+/-, 5-

References:

Change to alternative regimen before progression:

1. Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga JY, Gupta V, Costa R, Srock S, de Ducla S, Freuden sprung U, Mustacchi G. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1351-60.

Treatment until progression

1. Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, Amadori D, Wilcken N, D'Amico M, DeCensi A, Bruzzi P. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol. 2011;29:2144-9.
2. Alba et al. Breast Cancer Res Treat 2010
3. Park et al. JCO 2013

Chemotherapy for MBC – General Considerations: Drug Selection (8/18)

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

1. 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

1. 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.

1. 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 (9/18)

Further information and references:

1. O'Shaughnessy JA, Kaufmann M, Siedentopf F, Dalivoust P, Debled M, Robert NJ, Harbeck N. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. *Oncologist*. 2012;17:476-84.

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 than 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
-
1. 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.

1. 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

1. 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.

1. 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.
2. 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* (10/18)

Further information and references:

Consent:

Eribulin: 5++, 21+, 4+/-

1. Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA, Awada A. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. *Breast Cancer Res Treat.* 2014;148:553-61.

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 (*Gherzi 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 (*Gherzi 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 (11/18)

Further information and references:

1. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, Chollet P, Manikas A, Dieras V, Delozier T, Vladimirov V, Cardoso F, Koh H, Bougnoux P, Dutcus CE, Seegobin S, Mir D, Meneses N, Wanders J, Twelves C. 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.

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-) (12/18)

Further information and references:

Consent:

Carboplatin (vs. Docetaxel): 2++, 11+, 19+/-

Carboplatin in gBRCA mutation: 1++, 26+

Gemcitabin/Cisplatin (vs. GemPac): 1++, 18+, 10+/-

Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:

1. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) Tutt A, Ellis P, Kilburn L, Gilett C, Pinder S, Abraham J, Barrett S, Barrett-Lee P, Chan S, Cheang M, Fox L, Grigoriadis A, Harper-Wynne C, Hatton M, Kernaghan S, Owen J, Parker P, Rahman N, Roylance R, Smith I, Thompson R, Tovey H, Wardley A, Wilson G, Harries M, Bliss J. San Antonio Breast Cancer Symposium 2014; S3-01.

Gemcitabin/Cisplatin (vs. GemPac)

1. Gemcitabine with cisplatin or paclitaxel in metastatic triple-negative breast cancer. Xichun Hu, Binghe Xu, Li Cai, Zhonghua Wang, Biyun Wang, Jian Zhang, Yuee Teng, Zhongsheng Tong, Yueyin Pan, Yongmei Yin, Changping Wu, Zefei Jiang, Xiaojia Wang, Guyin Lou, Donggeng Liu, Jifeng Feng, Jianfeng Luo, Jiong
2. Wu, Zhimin Shao and Joseph Ragaz San Antonio Breast Cancer Symposium 2014; P3-10-02

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 $\geq 3/4$)

1. 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.

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (13/18)

Further information and references:

Consent:

Cap+Bev as maintenance after Doc+Bev: 1++, 3+, 22+/-, 4-
2nd line as treatment through multiple lines: 19+/-, 4-

Cap+Bev as maintenance after Doc+Bev:

1. Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga JY, Gupta V, Costa R, Srock S, de Ducla S, Freudensprung U, Mustacchi G. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:1351-60.

2nd line as treatment through multiple lines:

1. von Minckwitz G, Puglisi F, Cortes J, Vrdoljak E, Marschner N, Zielinski C, Villanueva C, Romieu G, Lang I, Ciruelos E, De Laurentiis M, Veyret C, de Ducla S, Freudensprung U, Srock S, Gligorov J. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1269-78.
2. 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.

3. 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
4. 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
5. 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.
6. 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
7. 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
1. 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:

1. 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 (14/18)

Further information and references:

Consent:

Taxanes + trastuzumab + everolimus: 4+/-, 21-, 5—

1. Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, Lin NU, Modi S, Patt DA, Perez EA, Perlmutter J, Ramakrishna N, Winer EP. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32:2078-99.

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.

1. 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)

1. 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
2. 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
3. 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
4. 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
5. 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+/-)

1. 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.
2. 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^a AGO+/-)

1. 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.
2. 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

Trastuzumab + aromatase inhibitors (if ER+) (LoE 2bB AGO+/-)

1. 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+/-)

1. 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) (15/18)

Further information and references:

T-DM1

1. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Dieras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
2. Baselga et al., December 7, NEJM 2011

2013

Capecitabine + lapatinib (LoE 1b B AGO+)

1. 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 JI, 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.
2. 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.

1. 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)

1. 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.
2. 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 +)

1. 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.”

1. 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:

1. 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:

1. 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 +)

1. 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 +)

1. 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 (16/18)

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 +/-)

1. 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).
2. 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.”

1. 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 +)

1. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Gruszfeld A, Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, Gorbounova V, Raats JI, 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.
2. 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 +)

1. 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
2. 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

1. Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in
2. HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. *ASCO* 2012
3. 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.
4. Baselga et al., Dec

Lapatinib in HER2-positive Metastatic Breast Cancer (17/18)

Further information and references:

Anthracycline and Taxane and Trastuzumab pre-treatment

1. Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG, Chan S, Jagiello-Gruszfeld A, Kaufman B, Crown J, Chan A, Campone M, Viens P, Davidson N, Gorbounova V, Raats JI, 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.
2. 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.
3. 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).
4. 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).
5. 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

1. 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)

1. 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.

Immunodiagnostic Tests and Immunotherapy (18/18)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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➤ **Versions 2002-2014:**

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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)	2b	C	+/-

Denosumab in Breast Cancer

Oxford / AGO LoE / GR

- | | | | |
|---------------------------------------|----|---|-----|
| ➤ Reduction of hypercalcemia | 1a | A | ++ |
| ➤ Reduction of skeletal complications | 1a | A | ++ |
| ➤ Reduction of bone pain | 1a | A | ++ |
| ➤ 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

Oxford / AGO LoE / GR

➤	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	++
➤	Zoledronate IV 4 mg q12w*	1b ^a	B	+
➤	Denosumab 120 mg s.c. q4w	1a	A	++
➤	Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis	5	D	--

*for patients after zoledronate iv 4 mg q4w for 1 year or longer

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Skeletal Metastases

Treatment with Radionuclids

**Oxford / AGO
LoE / GR**

- **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisite: hot spots in the bone scintigraphy)**
 - **¹⁸⁶Rhenium-hydroxyethylidene-diphosphonat**
 - **¹⁵³Samarium**
 - **⁸⁹Strontium**
 - **²²³Radium**

1b	B	+
2b	B	+
1b	B	+
1b	B	+
1b	B	+

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

Technical Aspects

Spine and limbs

Oxford LoE: 3b

GR: C

AGO: +

- **Marrow splints**
- **Plate osteosynthesis**
- **Compound osteosynthesis (replacement by PMMA and osteosynthesis)**
- **Vertebral replacement by titanspacer**
- **Tumor-Endoprothesis**
- **Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor**
- **Kypho-IORT (in studies only)***
- **Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)**

***Study participation recommended**

Metastatic Bone Disease: Radiotherapy (RT)

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Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
 - Single dose 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 after RT

Oxford / AGO
LoE / GR

Recurrent bone pain in pre-irradiated parts of the skeleton

➤ Single dose RT*	3b	C	++
➤ Fractionated RT*	3b	C	+
➤ Radionuclid therapy	3b	C	+
➤ Magnetic resonance-guided focused ultrasound	1b	B	+

*Dosing and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

**Oxford
LoE**

- **Renal function deterioration due to IV-aminobisphosphonates**
- **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3% / 1.8%)**
 - Association with (simultaneous) anti-angiogenetic therapies
- **Severe hypocalcemia (Dmab>BPs)**
- **Acute Phase Reaction* (IV Amino-BPs, Db) 10-30%**
- **Gastrointestinal side effects (oral BPs) 2-10%**
- **Atypical femur fractures**
 - absolute risk of 11 per 10,000 person years of BP use

1b

1b

3b

1b

1b

1b

2b

**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
- Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended

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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Dosage of Adjuvant Bisphosphonates for Improvement of Survival

➤ Non-Aminobisphosphonates:

➤ **Clodronate po 1600 mg/d (Bonefos/ Clodronic acid)**

➤ **Clodronate po 1040 mg/d (Ostac)**

➤ Aminobisphosphonates:

➤ **Zoledronate iv 4 mg/6 m (Zometa/ Zoledronic acid)**

➤ **Ibandronate po 50 mg/d (Bondronat/ Ibandronic acid)**

➤ **Pamidronate po (orally not available in most countries)**

➤ **Risedronate po 35 mg/w* (Actonel/ Risedronic acid)**

➤ **Alendronate po 70 mg/w (Fosamax/ Alendronic acid)**

➤ **Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2 - 5 years**

Aminobisphosphonates include:

Zoledronic acid (65%), Oral ibandronate (24%), Oral pamidronate (8%),
Oral residronate (2%), Oral alendronate (1%) (data from EBCTCG-metaanalysis)

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

**Oxford / AGO
LoE / GR**

➤ **Bisphosphonates**

➤ **Therapy**

1b B ++

➤ **Prevention**

1b A +

Denosumab

➤ **Therapy**

1b B ++

➤ **Prevention**

1b A +

➤ **Hormone replacement therapy**

5 D -

➤ **Regular BMD-measurement recommended (Intervals depending on 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)** | 4 | C | ++ |
| ➤ Vitamine D3 suppl. (800–2000 U/d) | 4 | C | ++ |
| ➤ Cessation of smoking, reduction of alcohol | 2b | B | ++ |
| ➤ 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/osteoporose-leitlinie-2014

**if nutritional supply is insufficient, (in combination with Vit D3 only)

www.ago-online.de

Further
Information

References

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 (improves spine only)	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**

****elevated risk of myocardial infarction. Substance restricted to postmenopausal pats. with severe osteoporosis and high risk of fractures**

<http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kitteltaschenversion%2015.12.2014.pdf>

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSE THERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.¹

Lebensalter in Jahren		T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.)				
Frau	Mann ²	-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

¹ Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).

² bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score^{3,4}, wenn:

- Glukokortikoide oral $\geq 2,5$ mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

Osteooncology and Bone Health (2/19)

No further information

No references

Bisphosphonates in Breast Cancer (3/19)

No further information

References:

First three statements:

Metaanalysen and Reviews (metastatic breast cancer):

1. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J; ESMO Guidelines Working Group Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014;25 Suppl 3:iii124-37.
2. Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. 2005;(2):CD003474.
3. Ross JR, Saunders Y, Edmonds PM et al. Systematic Review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ 2003 ;327 :469-474
4. Hillner BE, Ingle JN, Chlebowski RT. American Society of Clinical Oncology 2003 Update on the role of bisphosphonates and bone health issues in women with breast cancer, J Clin Oncol 2003; 21:4042-4057.
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Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/19)

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Metastatic Bone Disease Recurrent Bone Pain (11/19)

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TED-voting of the AGO-group (n=17): ++ n=1; + n=14; +/- n=2

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/19)

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Recommendations for Precautions to Prevent ONJ (13/19)

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Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (14/19)

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Dosage of Adjuvant Bisphosphonates for Improvement of Survival (15/19)

No further information

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Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (16/19)

No further information

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Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/19)

No further information

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<http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf>
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Medical Treatment of Osteoporosis (18/19)

No further information

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TED-voting of the AGO-group (n=25): ++ n=1; + n=15; +/- n=9

Guidelines of the DVO (19/19)

No further information

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<http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kurzfassung%20und%20Langfassung%2018.%2009.%202014.pdf>
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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 2003–2014:**
**Bauerfeind / Bischoff / Böhme / Brunnert / Diel
/ Fehm / Friedrich / Friedrichs / Gerber / Hanf /
Janni / Lück / Maass / Oberhoff / Rezai /
Schaller / Seegenschmiedt / Solomayer /
Souchon**
- **Version 2015:**
Bischoff / Diel

Specific Sites of Metastases

- **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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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 onset oligometastases**
- **Surgical treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus, occlusus, spinal cord compression**
- **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**

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Breast Surgery in Primary Metastatic Disease

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- | | | | |
|--|----------|----------|------------|
| ➤ Local treatment (R0) of primary tumor | 2 | B | +/- |
| ➤ Axillary surgery for cN1 | 5 | C | +/- |
| ➤ Sentinel in cN0 | 5 | C | - |

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Liver Metastasis

Local Therapy

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- **Resection of liver metastasis (R0)**
Individual cases (liver function) with resectable metastases
HR positive; chemotherapy sensible
- **Regional chemotherapy**
- **Regional radiotherapy**
(SIRT, radiochemoembolization, other modalities)
- **Thermoablation**
(RFA, LITT, cryotherapy)

3b C +/-

4 C +/-

3b C +/-

4 C +/-

3b C +/-

Pulmonary Metastases

Local Therapy

Oxford / AGO

LoE / GR

- **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

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➤ 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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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

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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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Weekly chemotherapy with*:

Epirubicin, Doxorubicin, Paclitaxel

4 D ++

Capecitabine

4 D ++

**HER2 pos.: add anti-HER2
Treatment**

5 D ++

* Consider pre-treatment

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Soft Tissue Metastasis

Local Therapy

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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 Primary 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.

References:

Resection of liver metastases:

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SIRT (selective internal radiation therapy):

1. Hoffmann RT, et al: Radiofrequency ablation after selective internal radiation therapy with Yttrium90 microspheres in metastatic liver disease-Is it feasible? Eur J Radiol. 2010 Apr;74(1):199-205

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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2. Bielsa S et al: Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung. 2011 Apr;189(2):151-5.
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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 aproval 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

1. Cases E, et al: Use of indwelling pleural catheter in the outpatient management of recurrent malignant pleural effusion Arch Bronconeumol. 2009 Dec;45(12):591-6.
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:

1. Sebastian M, et al: Treatment of malignant pleural effusion with the trifunctional antibody catumaxomab (Removab) (anti-EpCAM x Anti-CD3): results of a phase 1/2 study. J Immunother. 2009 Feb-Mar;32(2):195-202.

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:

1. Saâda E, et al: Pathogenesis and management of refractory malignant ascites. Bull Cancer. 2011 Jun;98(6):679-87.
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3. Petrelli F, Borgonovo K, Lonati V, Elia S, Barni S Regression of liver metastases after treatment with intraperitoneal catumaxomab for malignant ascites due to breast cancer. Target Oncol. 2012 Nov 30.

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.

References:

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.
2. Freyer G, et al: Palliative hormone therapy, low-dose chemotherapy, and bisphosphonate in breast cancer patients with bone marrow involvement and pancytopenia: report of a pilot experience. *Eur J Intern Med.* 2000 Dec 20;11(6):329-333.
3. Ardavanis A, et al: Low-dose capecitabine in breast cancer patients with symptomatic bone marrow infiltration: a case study. *Anticancer Res.* 2008 Jan-Feb;28(1B):539-41.
4. Krockenberger M, et al: Prolonged clinical benefit from platinum-based chemotherapy in a patient with metastatic triple negative breast cancer. *Eur J Gynaecol Oncol.* 2009;30(4):449-51. 2.

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:

1. Wilson B, et al: Resolution of extensive leptomeningeal metastasis and clinical spinal cord compression from breast cancer using weekly docetaxel chemotherapy. Breast Cancer Res Treat. 2012 Jan;131(1):343-6. Epub 2011 Oct 26.
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

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 the german registry study is 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**

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.

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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

Viani GA et al. BMC Cancer 2007, 7:53

Brain Metastases (1–3 Lesions)

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WBRT + SRS boost or neurosurgery (vs. WBRT)
Improved local control rate

2a B ++

SRS (lesions < 3 cm) or neurosurgery +/- WBRT*
WBRT**

2b B ++

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

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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 > ~ 3 cm 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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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

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 (>3 Lesions)

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- **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)**
- **T-DM1 (HER2 pos. disease)**
- **Re-radiation (if feasible)**

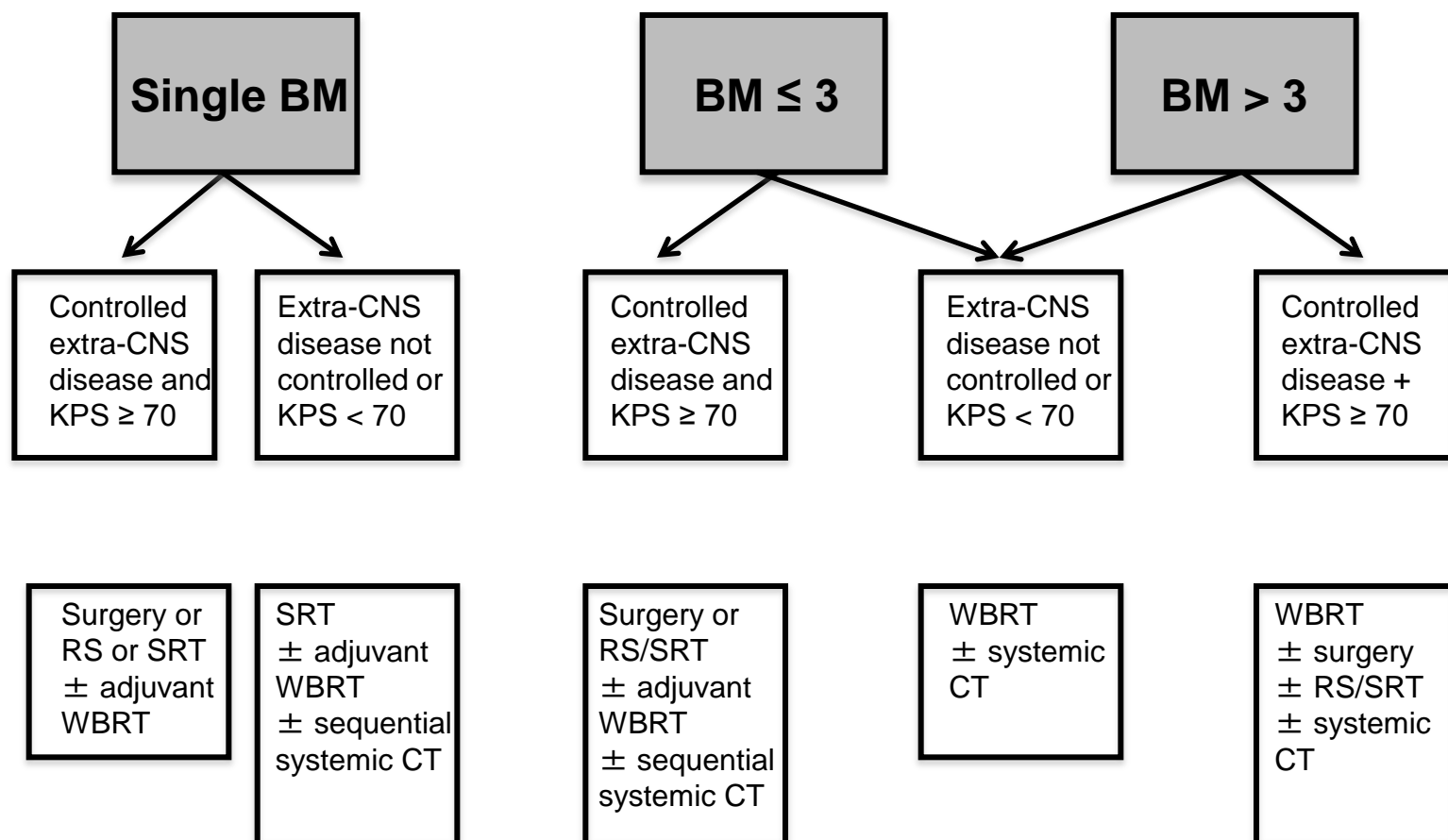
3a	D	+/-
2b	B	+
2b	B	+
3a	D	+/-

*Symptom adjusted therapy

Possible Treatment Approach for Brain Metastases (BM) in Breast Cancer*

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BM: brain met.
CT: chemotherapy

RS: radiosurgery
SRT: stereotactic radiotherapy

WBRT: whole brain radiotherapy

*Adapted from Bertolini F et al. CNS Oncology 2015;4(1):37-46

Systemic and Symptomatic Therapy of Brain Metastases

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- | | | | |
|--|----|---|-----|
| ➤ Continue anti-HER2-treatment in case of extracranial remission (HER2 pos. disease) | 2c | C | + |
| ➤ Lapatinib + Capecitabine as initial treatment (HER2 pos. disease) | 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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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 (HER2 pos. disease)	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 (2/13)

No further information

No references

CNS Metastases in Breast Cancer – Incidence (3/13)

No further information

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CNS Metastases in Breast Cancer (BC) Risk Factors (4/13)

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).

References:

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References: There is no evidence for BM-screening in asymptomatic BC-patients

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Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/13)

No further information

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Brain Metastases (1-3 lesions) (7/13)

No further information

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No further information

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Leptomeningeal Carcinomatosis Local Therapy (13/13)

No further information

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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 2002–2014:**
**Albert / Bauerfeind / Blohmer / Fersis /
Friedrich / Gerber / Göhring / Hanf / Janni /
Kümmel / von Minckwitz / Oberhoff / Scharl
/ Schmidt / Schütz/ Thomssen**

- **Version 2015:**
Hanf / Kümmel

„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*

General considerations

Oxford AGO

LoE / GR

- **Alternative methods (CAM)
instead of surgical treatment** 5 D --
- **Alternative methods (CAM)
instead of systemic treatment** 2b B --
- **While on anti-cancer treatment: beware of drug interactions**

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LEHREN
HEILEN

Complementary Therapy

Pre- and Postoperative

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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 -

Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

- **Mistletoe (*Viscum album*) in order to reduce side effects**
(influence on efficacy of anti-tumor therapy unknown)
- **Thymic peptides** (lowered risk of severe infections)
(influence on efficacy of anti-tumor therapy unknown)
- **Ginseng** (in order to reduce cancer related fatigue)
(note: ginseng inhibits cytochrome P enzymes
e.g. CYP 3A4)
- **Ganoderma Lucidum**
- **L-Carnitine** (given for prevention of toxicity, increased
chemotherapy induced peripheral neuropathy)
- **L-Carnitine does not improve cancer rel. fatigue**
- **Curcumin as an adjunct to reduce radio dermatitis**
- **Ginger for chemotherapy induced nausea & vomiting**
(consider interaction with anti-tumor drugs)

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1a B +/-

2a B +/-

2b C -

2b C -

1b B --

1b B --

1b B +/-

1b C +/-

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)

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Additional Complementary Therapy

Side Effects Related to Cancer Treatments

e.g. Chemotherapy

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➤ 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
- Cognitive dysfunction
- Fatigue
- Pain
- Leucopenia

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

Complementary Treatment

Mind-Body Medicine I

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MBSR (Mindfulness-Based Stress Reduction)

Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

1a 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, no higher risk of lymphedema

1a A ++

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Complementary Treatment

Mind-Body Medicine II

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- | | | | |
|---|----|---|-----|
| ➤ Yoga | | | |
| ➤ Improves sleep, quality of life, stress, anxiety, depression | 1b | A | + |
| ➤ Improves fatigue | 1b | A | +/- |
| | | | |
| ➤ Qi Gong | 2a | B | +/- |
| May improve quality of life, fatigue, mood | | | |
| | | | |
| ➤ Tai Chi | 2a | B | +/- |
| Improves quality of life, physical performance | | | |
| | | | |
| ➤ Hypnosis (in combination with cognitive training) | 1b | A | + |
| Improves fatigue and muscle weakness under radiation therapy, also reduces distress | | | |

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Modifiable Lifestyle Factors

Prevention of Recurrence I

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➤ 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/day)

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**, irrespective of HR-status (improves prognosis – DFS/OS)
- **Low fat diet** (improves prognosis – DFS and OS)
dietary counseling recommended,
- **Avoid high-fat dairy products**
- **Flaxseed/increased fibre intake**
- **Adherence to general nutrition guidelines (e.g. DGE, WCRF)**
- **Dietary extremes** (are associated with less favourable outcomes)

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1a A ++

1a A +

2b C +

2a B +

2a B ++

1b B - -

Further
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Complementary Treatment

Prevention of Recurrence III

Dietary Supplements – Herbal Therapies

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Post treatment vitamin/antioxidant supplements doesn't appear to be associated with increased risk of recurrence (beware of drug/treatment interactions)

Smokers on antioxidant supplements are at higher risk for lung cancer

➤ **For Prevention of BC Recurrence:**

➤ **Antioxidants**

➤ **Orthomolecular substances**
(Selenium, Zinc...)

➤ **Vitamine supplementation in pats on a balanced diet (esp. Vit C, E, D)**
➤ Artificial carotenoids appear to be associated with worse outcome

➤ **Proteolytic enzymes**
(Papain, Trypsin, Chymotrypsin)

➤ **Soy-food (natural source of phytoestrogenes)**
➤ Concentrates containing ≥ 100 mg) isoflavones

➤ **Black Cohosh (Cimicifuga racemosa)**

➤ **Mistletoe (Viscum album)**

➤ **Thymic peptides (impact on OS)**

➤ **Oxygen- and ozone therapy**

➤ **Antioxidant supplements (after completion of radiotherapy)**

➤ **Laetrile**

➤ **Cancer bush (Sutherlandia frutescens), Devil's claw**
(Harpagophytum procumbens), **Rooibos tea** (Aspalathus linearis),
Bambara groundnut (Vigna subterranean)

Oxford AGO
LoE / GR

2b	B	
1b	A	
2a	B	+/-
5	D	-
2a	B	+/-
2b	B	-
3b	B	-
2a	B	+/-
2a	B	-
2a	B	+/-
1b	C	-
2a	B	-
5	D	--
2b	B	+/-
1c	D	--
5	D	-

Complementary Treatment Cancer Pain Reduction

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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

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Complementary Therapy – Survivorship (2/14)

Further information:

Screened Data Sources:

Pubmed	2003 - 01/2015
ASCO	2003 – 2014
SABCS	2003 – 2014
EBCC	2003 – 2014
Cochrane library:	summary Jan. 2015:

External advice:

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Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references

Alternative Therapies (3/14)

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.

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General Considerations (4/14)

No further information

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Complementary Treatment: Cancer Pain reduction (14/14)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Gynecological Issues in Breast Cancer Patients

Gynaecologic Issues in Breast Cancer Patients

- **Version 2015:
Loibl / Gerber
(with contribution from Hanf / Kümmel und
Stickeler / Scharl)**

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Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

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- **Endocrine responsive disease**
(HT may increase risk)
- **Endocrine non-responsive disease**
(apparently no risk increase)
- **Endocrine responsive disease: combined
treatment TAM plus low-dose-HT**
- **Tibolone**
- **Topical vaginal application of**
 - **Estriol**
 - **Estradiol during AI therapy**

Oxford / AGO
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1b B -

2a B +/-

2b B +/-*

1b A - -

4 D +/-

4 C -

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***Study participation recommended**

Alternative Medical Approaches to Reduce Menopausal Symptoms

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Medical approaches:

- **Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients**

- 1st choice: venlafaxine

1a A +

- 2nd choice: desvenlafaxine

1b A +/-

- 3rd choice: sertraline, escitalopram

1b A +/-

- **Gabapentin (BC and TAM-use)**

1a A +

- **Pregabalin**

1b A +/-

- **Clonidin (BC and TAM-use)**

1a A +

- **MPA (i.m. 500 mg single shot)**
(most potent, but endocrine agent!)

1b A +/-

- **Vitamine E**

1b A -

“Herbal” Approaches to Reduce Menopausal Symptoms

While anti-cancer treatment: Beware of drug interactions!

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	1b	A	-
➤ Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease)			
➤ Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses no effect on hot flashes)	2b	B	+/-
➤ Black Cohosh for hot flushes	1b	A	-
➤ Black cohosh + St.John´s Worth	1b	B	+/-
➤ St. John´s Wort (in combination-therapy) (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)	1b	B	--
➤ Kava-Kava (Piper methysticum)	5	D	--
➤ Red Clover leaf (Trifolium pratense)	1b	B	+/-
➤ Dong Quai root (Angelica sinensis)	5	D	--
➤ Ginseng root (Panax ginseng or P. quinquefolius)	1b	B	-
➤ Bromelain + Papain + Selen + Lektin (for, AI induced joint symptoms)	3b	B	+/-

Alternative General Approaches to Reduce Menopausal Symptoms after BC I

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General approaches:

➤ Physical exercise	1b	B	+
➤ Mind Body-medicine (yoga, hypnosis, education, counselling)	1b	B	+
➤ Cognitive behavioral therapy (CBT)	1b	B	+
➤ Acupuncture			
Aromatase-inhibitor treatment induced arthralgia	2b	B	+
Hot flashes	1b	B	+
Depression	2b	B	+/-
Anxiety, Sleep	3b	C	+/-

(take note: no acupuncture in tumor bearing region, possibility of cell seeding)

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

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- **Ovarian Function Protection**
- **CT + GnRHa (Interaction with CT unclear)** **1b B +/-**
(GnRHa application > 2 weeks prior to chemotherapy)

Impairment of CT – effect cannot be excluded!

- **Fertility preservation counselling** **4 C +**
- **Fertility preservation with
assisted reproduction therapy** **4 C +**

Ovarian Function Preservation – Comparison of Randomized Trials

	ZORO	PROMISE	Munster et al. - US	POEMS
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years
Treatment	goserelin	triptorelin	triptorelin	goserelin
Start of treatment	>2 weeks prior to cht	>1 week 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	Ovarian failure at 2 yrs 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%	
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predicitive factor
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	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%
Median time to restoration of menses (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	n.d.
Cyclophosph. dose	4600 vs. 4700mg	4080 vs. 4008 mg	n.r.	n.a.

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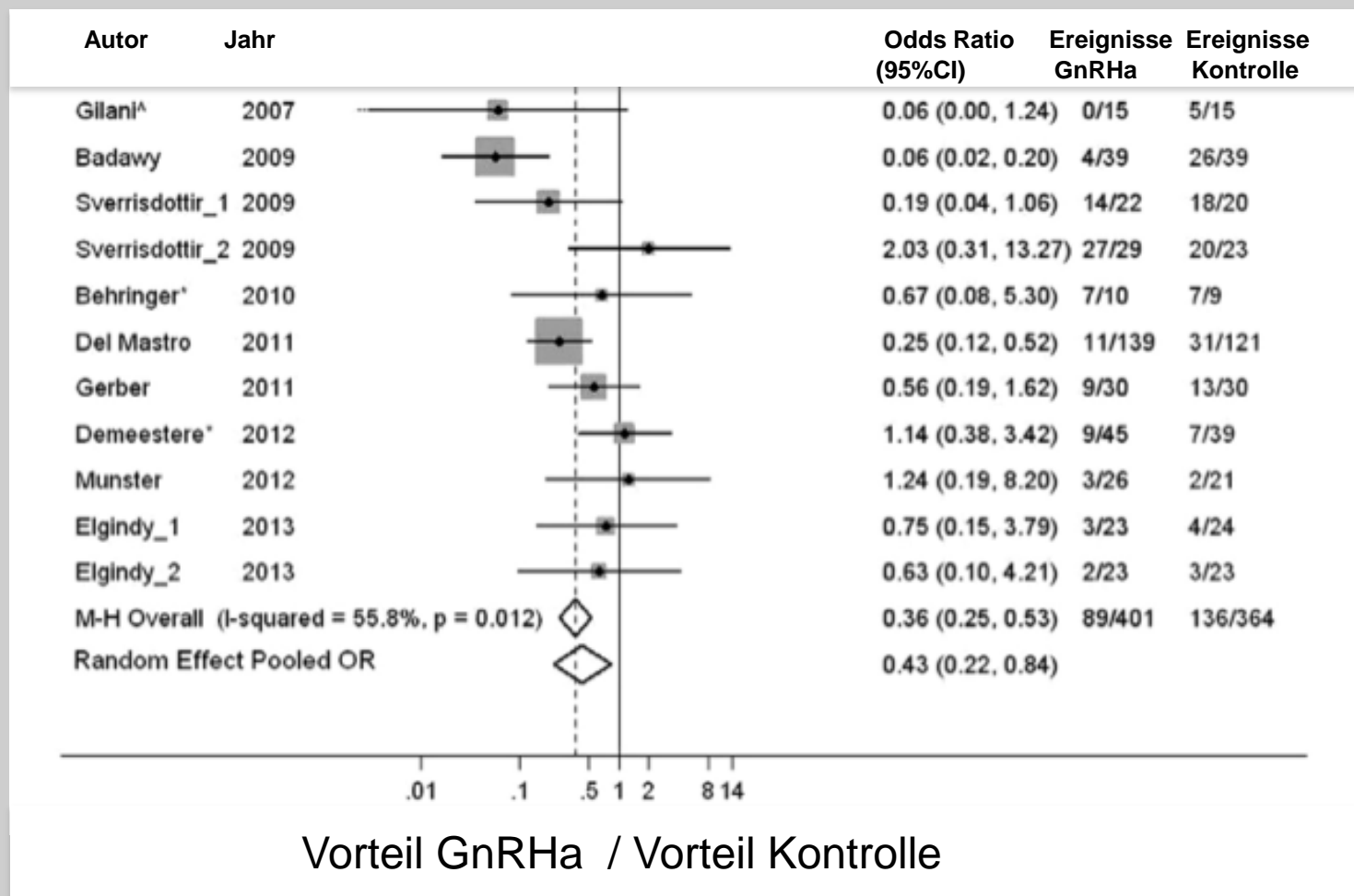
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Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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nach Del Mastro et al. Cancer Treat Rev 2014

Testing Ovarian Reserve

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Assessment of ovarian reserve in infertile patients (>6-12 mths without conception)*

5 C +

Tests for fertility assessment

- Anti-Müllerian Factor 3b B +/-
- Antral follicle count 3b B +/-

* Tests are suggested for women > 35 yrs and infertility for 6-12 months; the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated and infertility treatment may be considered.

Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserved (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268–273

Test	Details
FSH (follicle stimulating hormone) plus estradiol	<ul style="list-style-type: none"> • Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation
Anti Müllerian Hormone (AMH)	<ul style="list-style-type: none"> • No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation
Antral follicle count (AFC)	<ul style="list-style-type: none"> • Number of visible follicles (2–10 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.

Contraceptive Options for Women after Diagnosis of Breast Cancer

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➤ 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**

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References

Gynecological Issues in Breast Cancer Patients (2/12)

No further information

No references

Hormonal (Replacement) Therapy of Estrogen Deficiency after Diagnosis of Breast Cancer (3/12)

No further information

References:

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(HT may increase risk)
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Alternative Medical Approaches to Reduce Menopausal Symptoms (4/12)

Further information:

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. In breast cancer patients treated with tamoxifen and menopausal symptoms the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin is considered effective in treating hot flashes.(L'Espérance S, 2013) The use of paroxetine and fluoxetine should be avoided because they may reduce the efficacy of tamoxifen. Patients not being treated with tamoxifen the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes. Breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes.(Bordeleau L, 2010) For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl S, 2011). Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes.(L'Espérance S, 2013; Kontos M, 2010)

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SSRI:

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Gabapentin

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Pregabalin

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Clonidin

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(D) MPA (depo-) (Medroxyprogesterone acetate)

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Vitamine E

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“Herbal” Approaches to Reduce Menopausal Symptoms (5/12)

Further information and references:

The majority of studies, regarding the efficacy of herbal treatments for menopausal symptoms – mostly hot flushes – have not been conducted in women with breast cancer and many are of short duration.(Roberts H, 2010) Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating.(Ma H, 2011)

1. Roberts H: Safety of herbal medicinal products in women with breast cancer. *Maturitas*. 2010;66(4):363-9.
2. Ma H: 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;11:109.

Soy-derived isoflavonoids are potent **phytoestrogens**, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated.

1. Chen MN: Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric*. 2014 Dec 1:1-10. [Epub ahead of print]
2. Lethaby A: Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev*. 2013 Dec 10;12:CD001395.
3. Fritz H: Soy, red clover, and isoflavones and breast cancer: a systematic review. *PLoS One*. 2013;8:e81968.

Flaxseed has no effect on reducing hot flashes based on randomized phase III trial where it failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi S, 2012).

1. Flower G: Flax and Breast Cancer: A Systematic Review. *Integr Cancer Ther*. 2013 8;13(3):181-192.
2. Pruthi S: A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause* 2012: 19:48-53.

Taken together neither **Black cohosh** (*Cimicifuga racemosa*) (Leach MJ, 2012) nor **St John's Wort** (Caraci F, 2011) nor **Dong Quai** (Zhuang SR) nor **Ginseng root** (Kim MS. 2013) showed a benefit regarding improvement of menopausal symptoms. In a Phase III trial the fixed combination of Red Clover and St. Johns Wort were significantly better in reducing menopausal symptoms than placebo.

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3. Caraci F: Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. *Curr Drug Metab.* 2011 Jul 1;12(6):570-7.
4. Kim MS: Ginseng for managing menopause symptoms: a systematic review of randomized clinical trials. *J Ginseng Res.* 2013

In a recent randomised placebo controlled trial in 72 non breast cancer women suffering from hot flashes 40mg **red clover** leaves showed a significant reduction in hot flashes based on the menopausal rating scale compared to placebo.(Shakeri F, 2015)

1. Shakeri F: Effectiveness of red clover in alleviating of menopausal symptoms: A 12-week randomized, controlled trial. *Climacteric.* 2015 Jan 12:1-17. [Epub ahead of print]

A combination of **sodium selenite, proteolytic plant enzymes (bromelain and papain), and Lens culinaris lectin** as a complementary treatment was effective in reducing hormonal treatment related arthralgia and mucosal dryness. (Uhlenbrock B, 2010) But there were no reduction in other menopausal symptoms

1. Uhlenbruck B: Reduced side-effects of adjuvant hormone therapy in breast cancer patients by complementary medicine. *In Vivo.* 2010; 24(5):799-802.

Alternative General Approaches to Reduce Menopausal Symptoms after BC I (6/12)

Further information:

Physical exercises (PE) and cognitive behavioral therapy (CBT; this is one form of psychotherapy) have positive effects on menopausal symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause.(Duijts SF, 2012; Pachman DR, 2010; Mann E, 2012) Mind-Body-Medicine (MBM; Relaxation training, Yoga, Hypnosis) resulted in a moderate up to a significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation.(Buffart LM, 2012; Cramer H, 2014) However these effects are seen even after a longer period of application and avoid after some months stopping MBM. Acupuncture can also be used but the results from RCT are conflicting. A meta-analysis showed significant effects of acupuncture compared with sham acupuncture, but marked heterogeneity was observed in this model.(Lee MS, 2009)

References:

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4. Buffart LM: Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer. 2012 Nov 27;12:559.
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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/12)

Further information:

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

References:

Randomised Controlled Trials and Metaanalysis

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2. Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, Levaggi A, Giraudi S, Lambertini M, D'Alonzo A, Canavese G, Pronzato P, Bruzzi P. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun;40(5):675-83. doi: 10.1016/j.ctrv.2013.12.001.
3. Vitek WS, Shayne M, Hoeger K, Han Y, Messing S, Fung C Gonadotropin-releasing hormone agonists for the preservation of ovarian function among women with breast cancer who did not use tamoxifen after chemotherapy: a systematic review and meta-analysis. Vitek WS, Shayne M, Hoeger K, Han Y, Messing S, Fung C. Fertil Steril. 2014 Sep;102(3):808-815.

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Ovarian Function Preservation Comparison of Randomized Trials (8/12)

No further information

No references

Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure (9/12)

No further information

No references

Testing Ovarian Reserve (10/12)

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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3. Clemons M, et al: Identifying menopause in breast cancer patients: considerations and implications. *Breast Cancer Res Treat*. 2007 Aug;104(2):115-20.
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amenorrhea among premenopausal women with early stage breast cancer. *Cancer Invest.* 2008 Apr-May;26(3):286-95

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Assessment of Ovarian Reserve (11/12)

No further information

No references

Contraceptive Options for Women after Diagnosis of Breast Cancer (12/12)

No further information

References:

1. Backman T, Use of the levonorgestrel-releasing intrauterine system and breast cancer. Obstet Gynecol. 2005 Oct;106(4):813-7.
2. Strom BL, Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer. Contraception. 2004 May;69(5):353-60.
3. Moormann PG, Havrilesky LJ, Giersch JM et al. 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.

Diagnostik und Therapie von Patientinnen mit primärem und metastasierten Brustkrebs

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Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

◀ START

Prävention

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Version 2015.1D

- **Version 2011:**
Gerber / Thomssen
- **Version 2012–14:**
Dall / Diel / Maass / Mundhenke
- **Version 2015:**
Gerber / Mundhenke

Nicht-modifizierbare Risikofaktoren für Brustkrebs

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- **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

Modifizierbare Risikofaktoren für Brustkrebs

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

Präventiver Einfluss durch das Reproduktionsverhalten

Oxford / AGO
LoE / GR

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

2b B

2b B

2b B

3a B

Prävention durch Änderung von Lifestyle-faktoren: Gewicht / Glucosestoffwechsel

Oxford / AGO
LoE / GR

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

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

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

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	Oxford / AGO LoE / GR		
	2b	B	+
Bevorzugung einer gesunden Diät			
Nahrungszusammensetzung			
➤ Fettreduzierte Nahrung (ungesättigte > gesättigte Fettsäuren)	2a	B	+
➤ Verminderter Konsum an rotem Fleisch	2a	B	+
➤ Ergänzung von Vitaminen, Mineralien Spurenelem.	2a	B	-
➤ Vitamin-D-Substitution zur Prävention	3a	B	+/-
➤ Gemüse / Obst	2a	B	+/-*
➤ Phytoöstrogene / Soja	2a	B	+/-
➤ Ballaststoffreiche Ernährung	1b	A	+

*Empfohlen als Bestandteil einer gesunden Ernährung

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: Rauchen

Oxford / AGO
LoE / GR

- **Frauen, die nie geraucht haben , 2a B ++
haben ein verringertes Lebenszeit-
risiko für einen Brustkrebs
(~ 15-24% Reduktion)**
- **Junge Frauen haben ein 60% höheres Risiko für ein
Mammakarzinom, wenn sie > 10 Jahre vor der Geburt des
ersten Kindes geraucht haben (vs. Nichtraucherinnen)**

Prävention durch Änderung von Lifestylefaktoren: Körperliche Aktivität

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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 +

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⁽⁻⁾

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Brustkrebsrisiko und Prävention

START

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- **Versionen 2003–2014:**
**Schmutzler with Albert / Blohmer / Fehm /
Kiechle / Maass / Mundhenke / Rody /
Thomssen**
- **Version 2015:**
Schmutzler / Schmidt

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)

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 $\geq 10\%$**

BRCA1/2 Analyse in Patienten mit TNBC (unabhängig von der Familienanamnese)

BRCA1/2 Untersuchung in Patienten mit TNBC
sofern das Ergebnis Einfluss auf die
Therapieentscheidung hat

Oxford / AGO
LoE / GR

Unabhängig vom Alter*

3b C +

* **Studienteilnahme empfohlen**

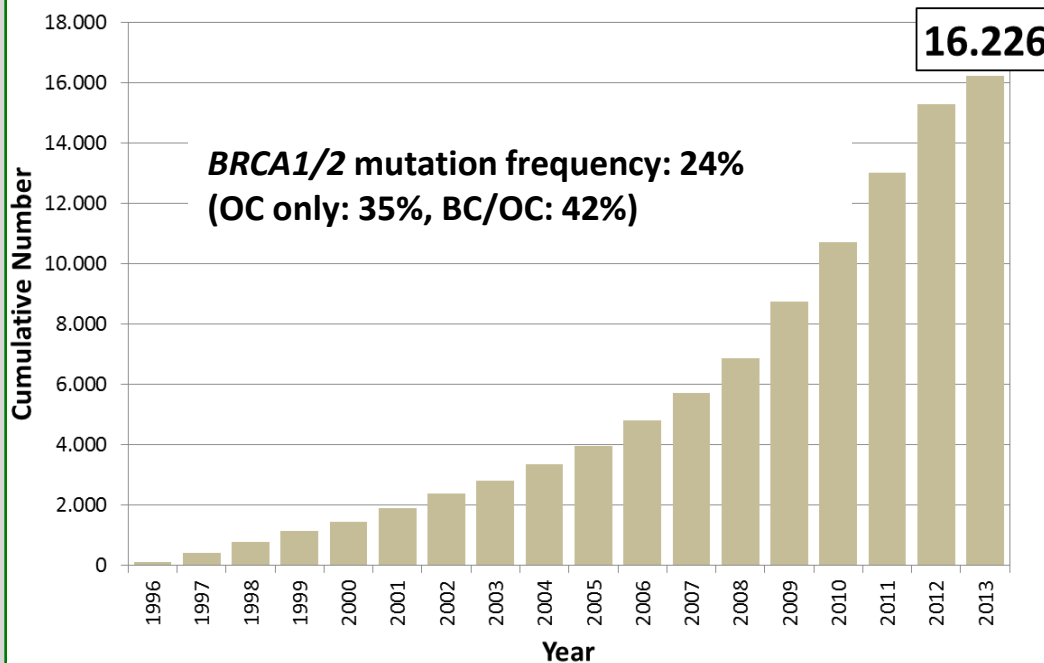
* Die *BRCA1/2* Mutationsnachweisrate sinkt mit steigendem Alter

Recruitment of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)

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18.875 in 2014; exp. +3.000 new families in 2015



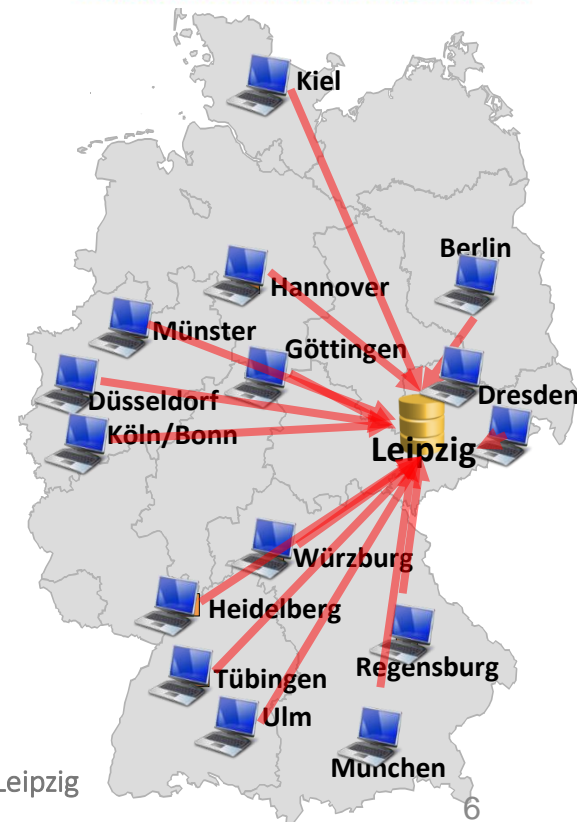
- since 1996, 15 centres
- national database (IMISE*, Leipzig)
- national DNA-biobank (center Cologne)

*Institute for Medical Genetics, Statistics and Epidemiology, Leipzig



**DEUTSCHES
KONSORTIUM**
für familiären Brust-
und Eierstockkrebs

unterstützt durch die Deutsche Krebshilfe e.V.



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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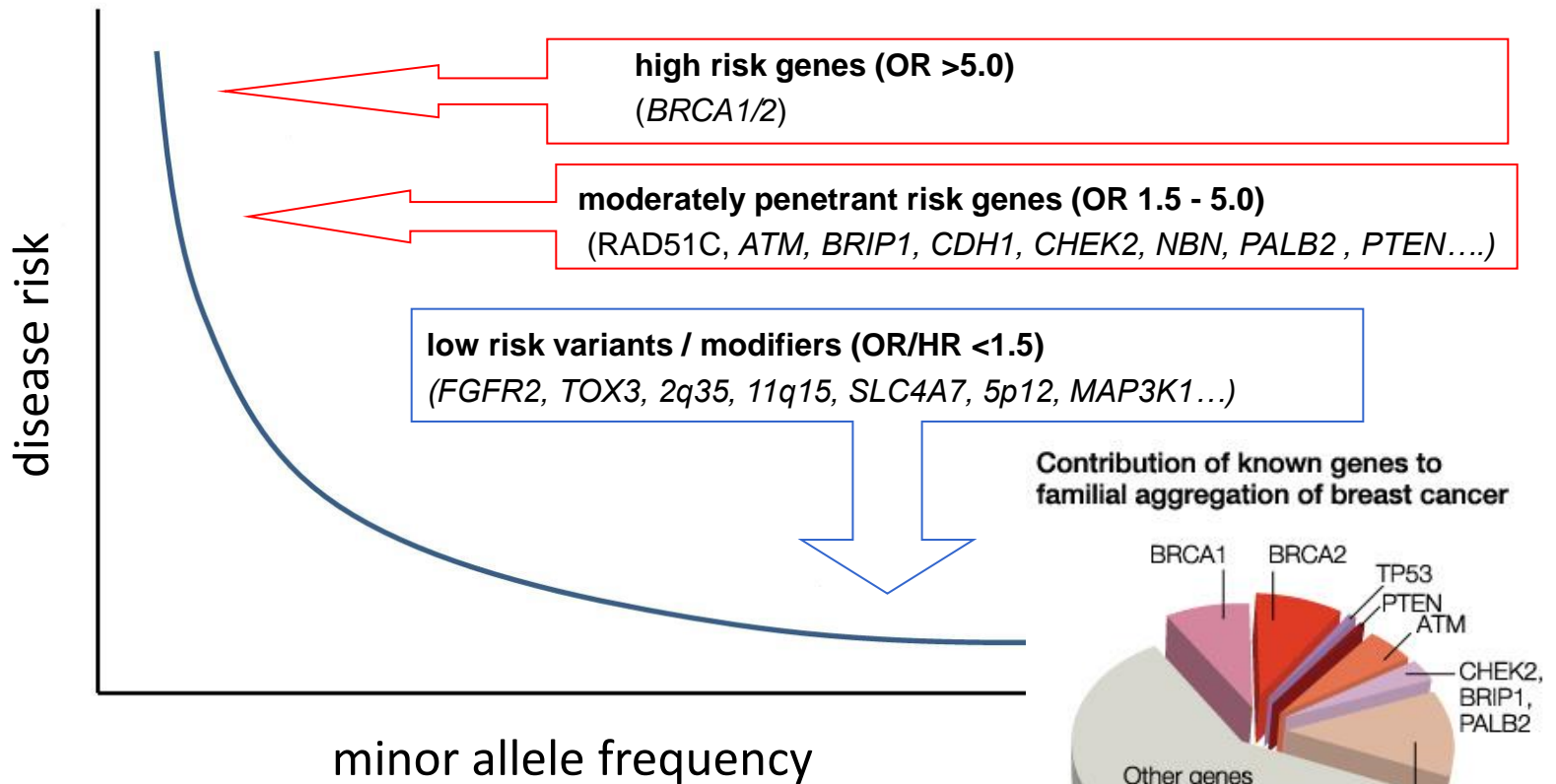
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LEHREN
HEILEN

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

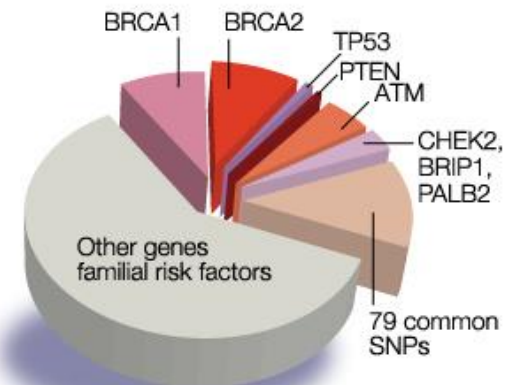
Stand der Forschung: Oligogenetischer Erbgang und genetische Heterogenität

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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 %

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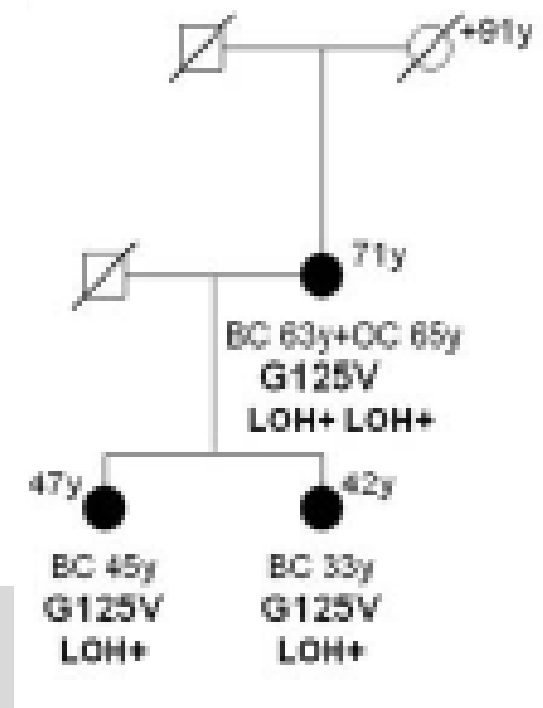
Empfehlung: genetische Beratung: GCP

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

TruRisk™ BC/OC Genpanel (34 Gene)

des Dt. Konsortiums

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ATM core gene	BRCA1 core gene	BRCA2 core gene	CDH1 core gene	CHEK2 core gene	NBN core gene	PALB2 core gene	RAD51C core gene
RAD51D core gene	TP53 core gene	MLH1 Lynch syndrome	MSH2 Lynch syndrome	MSH6 Lynch syndrome	PMS2 Lynch syndrome	ENIGMA #1	ENIGMA #2
ENIGMA #3	ENIGMA #4	ENIGMA #5	ENIGMA #6	ENIGMA #7	ENIGMA #8	ENIGMA #9	ENIGMA #10
ENIGMA #11	ENIGMA #12	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC	candidate GC-HBOC
candidate GC-HBOC	candidate GC-HBOC						

Genselektion:

- 10 BC/OC 'core genes'** (sufficient data for genetic counseling)
- 4 HNPCC genes** (~1% of unselected OC cases show truncating mutations; Song et al., 2014)
- 12 BC/OC 'research genes'** (validation in cooperation with the ENIGMA consortium)
- 8 candidate BC/OC genes** (GC-HBOC, unpublished)

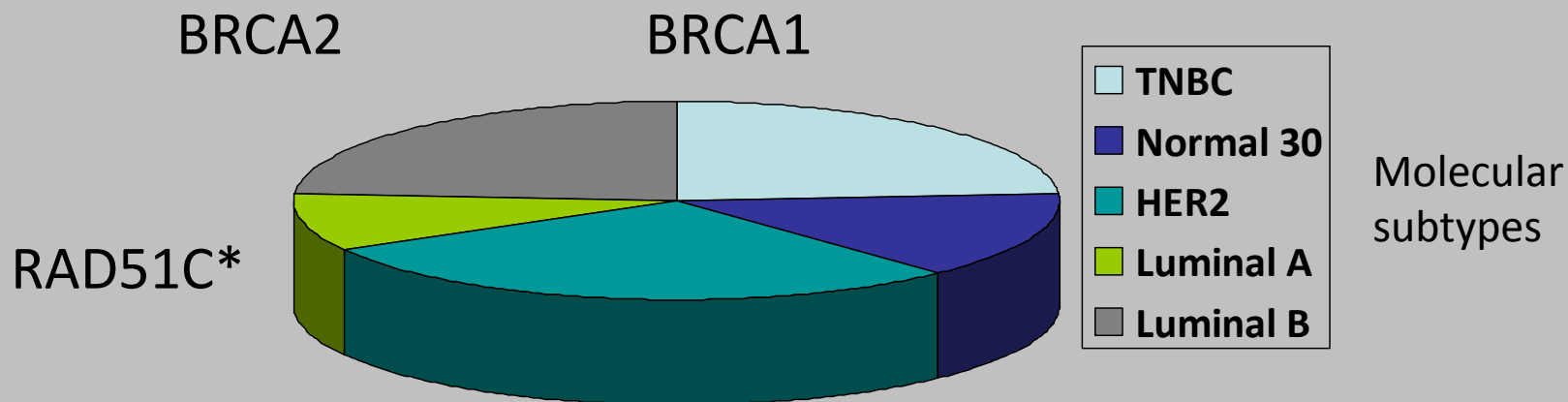
Strategie:

➤ Validierung in Kohorte, ständige Expansion und Verbesserung

Klinische Implikationen: Genotyp/Phenotyp-Korrelation

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*Meindl et al. Nat. Genet 2010

Gevensleben et al. 2014

➤ **Der Genotyp determiniert nicht nur die Erkrankungspenetranz sondern auch den klinischen Phänotyp und den Krankheitsverlauf**

Genetisch definierte Subtypen sind distinkte Tumorentitäten

Distinkte genetische Subtypen weisen distinkte klinische Merkmale auf. Daher sollten vor der Einführung klinischer Maßnahmen folgende Fragen geklärt werden:

- Krankheitspenetranz?
- Histologische Charakteristika?
- Sensitivität der Screening Verfahrens?
- Besseres Überleben bei früher Diagnosestellung?
- Natürlicher Krankheitsverlauf?
- Ansprechen auf Antitumorthherapie?

➡ **Genotyp-Phenotyp-Korrelationen müssen bekannt sein**

VUS: Probleme und Fragen

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- Die meisten VUS sind selten selten (≤ 3 , $>80\%$)
- Es sind zusätzliche Untersuchungen erforderlich, e.g. Spleißanalysen, funktionelle Analysen, Segregationsanalysen, co-occurrence Analysen, große Fall/Kontrollstudien
- *in silico* Vorhersageprogramme (e.g. PolyPhen2, SIFT, Mutation taster) sind für die klinische Entscheidungsfindung nicht adäquat bzw. nicht ausreichend
- Die VUS Klassifikation und klinische Entscheidungsfindung sind bisher nicht standardisiert

Niedrigrisikovarianten aus genomweiten Assoziationsanalysen (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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Niedrigrisikovarianten als modifizierende Faktoren bei BRCA-Mutationsträgerinnen

Retrospektiv

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%)

Prospektiv

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

Gegenwärtige klin. Bedeutung weiterer Risikogene

Weitere moderate und niedrig penetrante Gene und Allele werden vermutlich durch einen oligo- oder polygenen Erbgang übertragen

Moderate Risikogene wie RAD51C sind selten mutiert und scheinen mit spezifischen Tumorsubtypen assoziiert zu sein

Niedrigrisikovarianten erhöhen das Risiko nur unwesentlich. Sie scheinen aber multiplikativ zu wirken, sodass die Analyse eines Panels zukünftig von klinischer Relevanz werden kann.

Derzeit sollten moderate und niedrig penetrante Gene und Allele daher nur im Rahmen von prospektiven Kohortenstudien wie der des deutschen Konsortiums untersucht werden

.

	Oxford / AGO LoE / GR		
➤ Genetische Analyse von moderaten Risikogenen e.g. Genpanel	2b	B	-
➤ Genet. Analyse von Niedrigrisikoallele	3b	D	--
➤ Zuweisung an spezialisierte Zentren des Konsortiums oder kooperierende Zentren	5	D	++

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

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 moderatem und hohem Erkrankungsrisiko

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

**Oxford / AGO
LOE / GR**

1a A ++

2b B +

2a B ++

Multimodales Früherkennungsprogramm bei Frauen mit BRCA1/2 Mutation*

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			Oxford / AGO LOE / GR		
			2a	B	++
➤ Zum Nachweis früher Tumorstadien					
➤ Ärztliche Tastuntersuchung	>=25 Jahre		halbjährlich		
➤ Ultraschall	>=25 Jahre		halbjährlich		
➤ Mammographie	>=40 Jahre		1-2jährlich		
➤ Kernspintomographie	>=25 Jahre		jährlich		
➤ Zur Mortalitätsreduktion			4	C	+

*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

Oxford / AGO
LoE / GR

- **Eine sekundär prophylaktische unilatertale oder bilaterale Mastectomie ist ohne das Vorliegen von genetischen Risikofaktoren nicht indiziert**

2a

B +*

Chirurgische Prävention bei gesunden BRCA1/2 Mutationsträgerinnen

Oxford / AGO
LOE / GR

- **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

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	Oxford / AGO LoE / GR		
➤ 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	++*
➤ Bilateral mastectomy+ (RR-BM) reduces cl BrCa incidence	2b	B	+/-*
➤ Tamoxifen (reduces cl BrCa incidence)	2b	B	+/-*
➤ Indication for PBM should consider age at onset of first breast cancer and the affected gene + Overall prognosis has to be considered	2a	B	+++*

***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	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.

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⁺

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

**Oxford / AGO
LOE / GR**

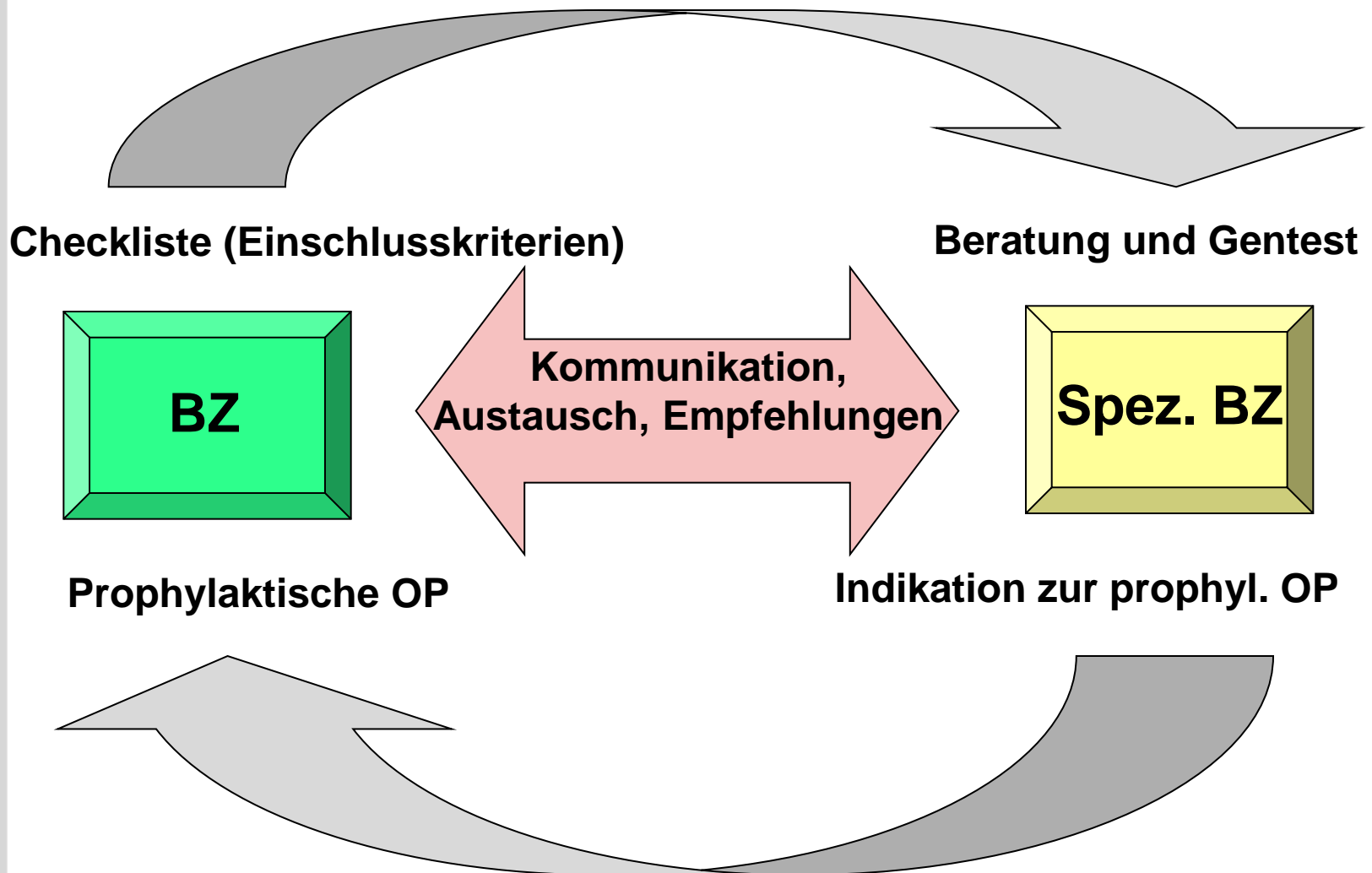
- **Brusterhaltende OP:
Adäquate lokale Tumorkontrolle (~10 Jahre Follow-up)** **2a B +**
 - **Systemische Therapie nach den allgemeinen Standards** **3a B +**
 - **BRCA1 Mutationsstatus ist ein prädiktiver Faktor für
das Ansprechen auf Chemotherapie** **3b B +**
 - **Carboplatin (vs. Docetaxel) bei metastastasiertem
Mammakarzinom** **2b^a 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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LOE / GR

➤ **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***

**Oxford / AGO
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

START

Früherkennung und Diagnostik

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- **Version 2005–2014:**
**Albert / Blohmer / Fersis /
Junkermann / Maass / Scharl /
Schreer**

- **Version 2015:**
Schreer / Albert

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

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)	

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Früherkennung Sonographie

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LOE / GR**

- **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	++
2b	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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	Oxford / AGO LOE / GR		
➤ Klinische Untersuchung	3b	B	++
➤ Mammographie	1b	A	++
➤ Tomosynthese (vs Spotkompression)	2b	B	+
➤ Sonographie	2b	B	++
➤ Elastographie (Shear wave)	2b	B	+
➤ Autom. 3D-Sonographie	3b	B	+/-
➤ MRT*	2b	B	+/-
➤ Minimalinvasive Biopsie	1c	A	++

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

Prätherapeutische Abklärung und Staging

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➤ 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

- **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)]**

N Houssami et al. Ann Surg 2013; 257

MRT Screening (Hoch-Risiko-Gruppe) Nutzen

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

MRT Screening bei Frauen mit hohem familiärem Risiko

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				MRT		Mammographie	
Autor	Hochrisiko / Mutation	Anzahl Frauen	Anzahl Karzinome	Sensitivität (%)	Spezifität (%)	Sensitivität (%)	Spezifität (%)
Kriege 2004	M	1909	50	80	90	33	95
Warner 2004	M	236	22	77	95	36	99
Hagen 2004	M	491	25	86	-	50	-
Leach 2005	H / M	649	35	94	77	40	93
Riedl 2007	H / M	327	28	50	98	85,7	92
Kuhl 2010	H / M	687	27	93	98,4	33	99,1
Rijnsburger 2010	M	594	97	77,4	89,7	41	-
Sardanelli 2011	H / M	501	52	91	97	50	-
Passaperuma 2012	M	496	57	90	97	19	97
Gareth 2014	H / M	649	139	93	63	60	-

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

Prospective study results for MRI screening in women with high familiar risk (H) and mutation carriers (M)

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%

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.“

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Pathologie

Pathologie

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- **Versionen 2004–2014:**
**Costa / Fehm / Friedrichs / Huober /
Kreipe / Lück / Sinn / Thomssen**
- **Version 2015:**
Sinn / Friedrichs

Allgemeine Prinzipien der histopathologischen Untersuchung beim Mammakarzinom

- **Jede Aussage in der histologischen Diagnose steht unter der Prämisse der klinischen Relevanz**
- **Die angewandte Nomenklatur richtet sich nach aktuellen Leitlinien und internationalen Klassifikationen**
- **Qualitätssichernde Maßnahmen sind auf allen Bereichen der pathologischen Diagnostik erforderlich**

Präanalyse: Fixation

Oxford / AGO
LoE / GR

- | | | | |
|---|----------|----------|-----------|
| ➤ Minimierung der Zeit bis zur Fixation (kalte Ischämiezeit) | 5 | D | ++ |
| ➤ Einhaltung einer minimalen Fixationszeit von 6 Stunden zur Gewährleistung einer optimalen Antigenerhaltung | 5 | D | ++ |
| ➤ Optimale Fixationszeit bei Stanzbiopsien: 6 - 72 h | 5 | D | ++ |
| ➤ Optimale Fixationszeit bei Resektaten: 12 - 72 h | 5 | D | ++ |
| ➤ Verwendung neutral gepufferter Formalinlösung | 5 | D | ++ |

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**FORSCHEN
LEHREN
HEILEN**

Indikationen der 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**

Aufarbeitung: Makroskopie und Präparateradiographie

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- **Berücksichtigung der präoperativen Befunde (z.B. multiple Herde, intraduktale Komponente, Bezug zu Nachbarstrukturen) bei der Makrodokumentation**
- **Routinemäßige Dokumentation klinisch relevanter Befunde durch Skizze oder Foto, unter Berücksichtigung der Topographie**
- **Präparateradiographie bzw. Scheibenradiographie bei nicht palpablen Läsionen und Mikroverkalkungen**

Aufarbeitung: Stanzbiopsien (Ultraschall gesteuert / stereotaktisch)

Oxford / AGO
LoE / GR

- **Aufarbeitung in Schnittstufen
(14G: min. 3 Stufen / 11G, 8G: 6-8 Stufen)**
- **Radiologisch-pathologische Korrelation
(Mikrokalk / Dichte), Anwendung der
B-Klassifikation**
- **Schnellschnittdiagnostik an Stanzbiopsien**
- **Evaluation des ER/PgR und HER2-Status**
- **Umlaufzeit < 24 h (Dignität)**

5 D ++

1b B ++

5 D - -

3b C ++

5 D +

Aufarbeitung: Brusterhaltende Therapie

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➤ 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: Mastektomie

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- **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 ++

Aufarbeitung: Sentinel-Lymphknoten

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➤ 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	-

Aufarbeitung: Intraoperative pathologische 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 | + |

Befundung: Histologischer Tumortyp

Oxford
LoE / GR

AGO

3b

C

++

➤ Histologischer Tumortyp entsprechend WHO-Klassifikation (4. Aufl. 2012)

- **Partielle spezielle Differenzierung:**
 > 50% NST-Komponente
 und < 50% spezieller Tumortyp
 (Minorkomponente)
- **Gemischte Differenzierung:**
 > 50% spezieller Tumortyp
 und < 50% NST-Komponente
 Beispiel: Muzinöses Mamma-Ca, Mischtyp
- **Reine Typen:**
 > 90% des Tumors vom speziellen Typ
 Beispiel: tubuläres oder kribriiformes Ca.

Befundung: Differenzierungsgrad

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➤ Anwendung des Nottingham-Grading (Elston & Ellis 1991) für alle Typen des invasiven Mammakarzinoms	5	D	++
➤ Bei sehr wenig Tumorgewebe rein nukleäres Grading oder Heranziehung zusätzlicher Kriterien wie Ki-67 Proliferationsfraktion	5	D	++
➤ Grading des DCIS gemäß WHO-Klassifikation des Mammakarzinoms (4. Aufl., 2012)	5	D	++
➤ Wiedergabe des Tumorgrading zumindest auch numerisch (z.B. G3)	5	D	++

Befundung: Tumorgröße und Tumorausdehnung

Oxford
LoE / GR

AGO

- **Invasive Tumorgröße, unter Berücksichtigung des makroskopischen und histologischen Befundes und klinisch-bildgebender Befunde**
- **Bei Satellitenherden und Multifokalität zusätzlich Gesamtausdehnung des invasiven Karzinoms**
- **Angabe der Ausdehnung der DCIS- oder LCIS-Komponente, wenn extensiv (mehr als 2x invasives Ca)**

5 D ++

5 D ++

5 D ++

Befundung: pTNM

Oxford
LoE / GR

AGO

5 D ++

➤ Anwendung der aktuellen UICC-Klassifikation (7. Auflage)

pT 1 - 3: Größter invasiver Tumorherd, nicht Gesamtausdehnung

pT4: Alleinige Infiltration der Dermis nicht ausreichend. Kriterien für pT4a/b/c/d müssen erfüllt sein

pT4d: Eine negative Hautbiopsie schließt pT4d (inflammatorisches Karzinom) nicht aus

pM: pM1 bei jeglichem nicht regionärem Tumornachweis, ausgenommen kontralateralem Zweitkarzinom. Eine Angabe von MX wird nicht empfohlen.

Befundung: Beurteilung der Resektionsränder, R-Klassifikation

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

- **Randsituation, makroskopisch Abstand zu allen Rändern und histologisch die nächsten < 1cm untersuchen**
- **Angabe des min. histologischen Sicherheitsabstandes und Topographie davon**
- **R-Klassifikation**

5	D	++
5	D	++
5	D	++

R0: Kein Residualtumor

R1: Histologisch invasives oder nicht invasives Karzinom im Resektionsrand

RX: Beurteilung des Resektionsrandes nicht möglich (z.B. Tumor in mehreren Teilpräparaten)

Befundung: Lymphgefäßinvasion

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	Oxford LoE / GR	AGO
➤ L1: Nachweis einer Lymphgefäßinvasion L0: Keine eindeutige Lymphgefäßinvasion	5 D	++
➤ IHC zum Nachweis einer Lymphgefäßinvasion	3b C	-
➤ Unterscheide: peritumorale und ausgedehnte Lymphgefäßinvasion	3b C	++
➤ Angabe der Blutgefäßinvasion (V0/V1) fakultativ, da prognostische Relevanz unklar	5 D	+

Befundung: Evaluation tumor-infiltrierender Lymphozyten (TIL)

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

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

- **Identifikation von Tumoren mit prädominantem lymphozytärem Infiltrat (> 50%) im Tumorstroma (n. Salgado et al.*)**

Nur das intratumorale Infiltrat im Stroma und an der Invasionsfront berücksichtigen

Zentrale Fibrose- und Nekrosezonen nicht bewerten

Durchschnittswert des lymphozytären Infiltrates in Prozent angeben

*Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Annals of Oncology*

Befundung: nach neoadjuvanter Chemotherapie

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	Oxford LoE / GR	/	AGO
➤ Identifikation des Tumorbetts, sonst ypTX	4	D	++
➤ Angabe der Tumorgröße (max. Tumorbettgröße mit vitalem, invasiven Ca.)	4	D	++
➤ pCR definiert als Fehlen invasiven Karzinoms sowie Abwesenheit von Gefäßinvasion und Lymphknotenmetastasen. Vorhandensein von pTis ist anzugeben.	2b	D	+
➤ IHC zum Nachweis minimalen Residualtumors	4	D	+/-
➤ Angabe von ypTN-Status nach CHT	5	D	++

Zusatzuntersuchungen: Bestimmung des ER mittels IHC

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- Immunohistochemischer Nachweis am Paraffinschnitt
- Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 1\%$)
- Angabe der Färbeintensität (0 - 3)
- Allred Score (0–8), Remmele Score (0 - 12)
- Reevaluation am Exzidat, wenn unklarer Befund an der Stanze oder triple-negativer Tumor

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LoE / GR

1a A ++

1a A ++

4 D +

4 D +

5 D +

Zusatzuntersuchungen: Bestimmung des PgR mittels IHC

Oxford / AGO
LoE / GR

- | | | | |
|--|----|---|----|
| ➤ Immunohistochemischer Nachweis am Paraffinschnitt | 1a | A | ++ |
| ➤ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 10\%$) | 1a | A | ++ |
| ➤ Angabe der Färbeintensität (0 - 3) | 4 | D | + |
| ➤ Allred Score (0–8), Remmele Score (0 - 12) | 4 | D | + |

Zusätzliche Untersuchungen: Molekulare Bestimmung von ER/PgR

Oxford / AGO
LoE / GR

- **Bestimmung der Hormonrezeptoren auf Einzelgenebene durch validierte Genexpressions-Testkits**
- **Bestimmung der Expression der Hormonrezeptoren durch RNA-Sequenzierung**
- **Verwendung der molekularen Rezeptorbestimmung zur Subtypisierung**

3b A +/-

5 D -

3b A +

Zusatzuntersuchungen: HER2 Bestimmung

Oxford / AGO
LoE / GR

1a A ++

- **Immunohistochemie (IHC):**
 - 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)
- **Einfarben In-Situ-Hybridisierung (ISH):** HER2+ wenn ≥ 6 Signale in mindestens 20 kohäsiven Zellen, negativ bei < 4 Signalen/Kern
- **Zweifarben ISH:** HER2+ bei Signal Ratio HER2:CEP17 ≥ 2,0 und/oder HER2-Signale ≥ 6
- **Uneindeutiges Ergebnis (2+ IHC, ≥ 4 - < 6 HER2 Signale ISH):** Retestung mit anderer Methode oder an anderem Block
- **Validierung der Immunohistochemie an Stanzbiopsien**

3a C ++

3a C ++

3a C ++

5 D ++

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

Zusätzliche Untersuchungen: Molekulare Bestimmung von HER2

Oxford / AGO
LoE / GR

- | | | |
|---|-------------|------------|
| ➤ Therapieentscheidungen sollten nur auf ISH und ISH basieren | 1a A | ++ |
| ➤ Bestimmung des HER2-Status durch validierte Genexpressions-Testkits | 3b B | +/- |
| ➤ Bestimmung der HER2-Amplifikation durch NGS | 5 D | - |
| ➤ Verwendung der molekularen HER2-Bestimmung zur Subtypisierung | 3b B | +/- |

Zusatzuntersuchungen: Ki-67 Bestimmung

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➤ Auszählung von Zellkernen an der Invasionsfront des Tumors	5	D	++
➤ Berücksichtigung auch schwach positiver Zellkerne	5	D	++
➤ Angabe des Ki-67 positiver Tumorzellen in Prozent	5	D	++
➤ Etablierung laborinterner Standards und Schwellenwerte	5	D	++
➤ Bildanalyse zur Objektivierung der Ki-67 Auszählung	5	D	+

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 immunohistochemischer 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

Qualitätssicherung: Immunhistochemie

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- **Verwendung einer automatisierten Färbeplattform**
- **Teilnahme an Ringversuchen**
- **Strikte Einhaltung und Monitoring der Vorgaben für die Präanalytik (Fixation)**
- **Verwendung von On-Slide-Kontrollen**
- **Plausibilitätskontrollen (z.B. Tumortyp, Grading)**

Qualitätssicherung: HER2-Bestimmung

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- **Laufende Dokumentation der HER2-Befunde**
- **Qualitätsziel: HER2-Positivitätsrate 15% - 20%**
- **Verwendung standardisierter und validierter HER2-Testkits**
- **Teilnahme an Ringversuchen**

Qualitätssicherung: Befundung

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- **Verantwortlichkeit der Befundung bei ein bis zwei in der Mammapathologie spezialisierten Pathologen**
- **Regelmäßige interdisziplinäre Befundbesprechungen mit radiologisch-pathologischer Korrelationsdiagnostik**
- **Teilnahme an Qualitätszirkeln**

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Prognostische und prädiktive Faktoren



Prognostische und prädiktive Faktoren

- **Versionen 2002–2014:**
**Costa / Friedrichs / Gerber / Göhring /
Harbeck / Liedtke / Loibl / Mundhenke /
Nitz / Rody / Schaller / Schmidt /
Schmutzler / Schneeweiss / Simon /
Solomayer / Thomssen**
- **Version 2015:**
Fersis / Janni

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”

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	++
➤ Übergewicht (BMI > 30 kg/m ²)	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

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	Direct hybridization
Central lab	Yes	yes	no	no
Indication and population studied	prognostic N-/+, <61 Jahre	prognostic N-/+, ER+ endocrine treated	prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated	prognostic postmenopausal N-/+, 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	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	yes	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	-
➤ Multigene assay (EndoPredict®, Prosigna®, Oncotype DX®) \$ (N-/+, HR+ HER2-)	I	B	+*
➤ 70 gene signature (MammaPrint®), N-/+	II	C	+*
➤ IHC4 (central pathology, published algorithm) #	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 systemische Therapie Therapieprädiktion I

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Faktor	LoE ₂₀₀₉	CTS	GR	AGO
➤ Multigensignatur (Mammaprint, Endopredict Oncotyp Dx, PAM50 Prosigna^{\$})	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumour infiltrating Lymphocytes	II	B	B	+/-
➤ PIK3CA mutation	II	B	B	+/-

^{\$} 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	+/-
➤ Übergewicht (BMI >30 kg/m²)	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	+
➤ Frühes Therapieansprechen (3 Wo.)	I	B	+
➤ Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen	I	A	-*

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 2005–2014:**
**Albert / Audretsch / Brunnert / Fersis /
Friedrich / Gerber / Kreipe / Nitz / Rody /
Schreer / Sinn / Thomssen**
- **Version 2015:**
Kreipe / Thomssen

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
 - Atypisches Papillom, wenn unvollständig entfernt
 - Radiäre Narbe, komplexe sklerosierende Läsion

Haupttypen der B3-Läsionen und prospektiver prädiktiver Wert (PPV) für Malignität (DCIS/invCa) im Resektat

B3-Läsionen:

~PPV

➤ Atypische ductale Hyperplasie (ADH)	40-50%
➤ Lobuläre intraepitheliale Neoplasie (LN/LIN)	0-20%
➤ Flache epitheliale Atypie (FEA)	15%
➤ Radiäre Narbe	3%
➤ Komplexe sklerosierende Läsion	3%
➤ Papillome ohne Atypien	0%
➤ Zelluläre fibroepitheliale Tumore / Phyllodes Tu.	0%

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Management nach minimalinvasiver Biopsie

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LoE / GR

➤ 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, atypische epitheliale Proliferation vom ductalen Typ (ADP)
- 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 (duktale intraepitheliale Neoplasie Grad 1 - 3) ist nicht ausreichend validiert.

Strategie nach Diagnose einer ADH in der Nadelbiopsie

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ADH in Stanz-/ Vakuumbiopsie:

- offene Exzisionsbiopsie
- offene Exzisionsbiopsie verzichtbar unter der Voraussetzung
 - a) Nur geringe Atypien
 - b) Kleiner Herd (≤ 2 TDLU* in Vakuumbiopsie)
 - c) Suspekte Läsion in der Bildgebung komplett entfernt

3a C ++

5a C +

ADH im Resektionsrand:

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

3a C ++

*TDLU = terminale duktulo-lobuläre Einheit

Brustkrebsrisiko nach ADH

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

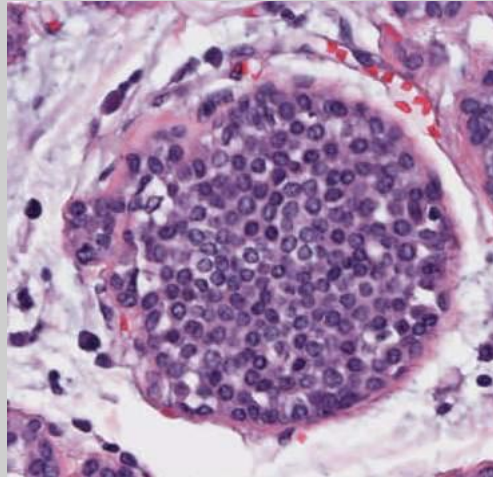
Lobuläre intraepitheliale Neoplasie (LIN)

- Umfasst: 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

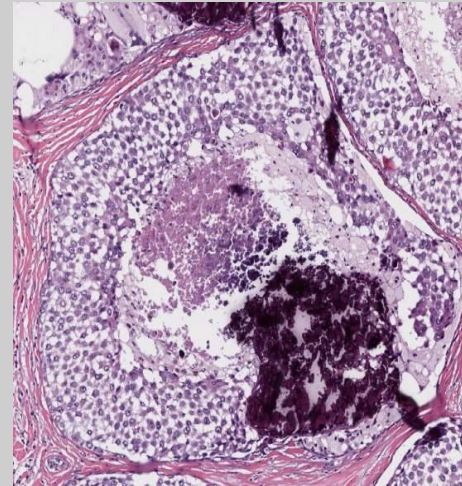
Formen des LCIS

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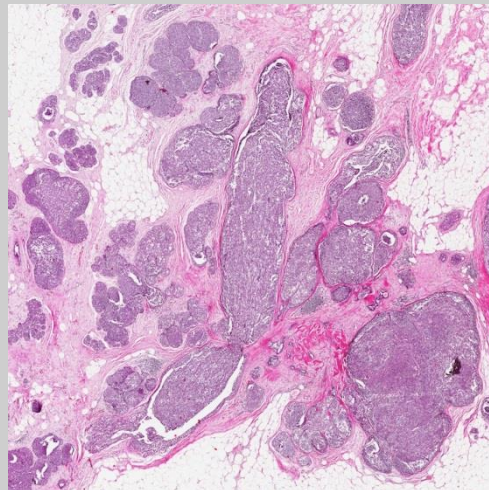
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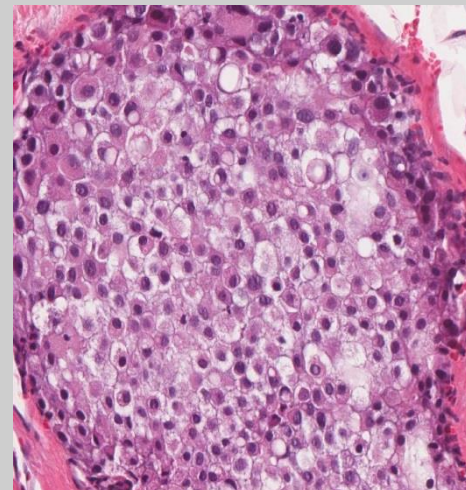
Klass. LIN



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

**Oxford / AGO
LoE / GR**

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

→ Offene Biopsie

3b C +

→ Auf offene Biopsie kann verzichtet werden
unter der Voraussetzung, dass:

a) kleinherdiger Befund (≤ 2 TDLU* in Vakuumbiopsie)

und

b) vollständige Entfernung der auffälligen
Läsion in der Bildgebung

5 C +

➤ **FEA im Resektionsrand nach Exzisionsbiopsie:**

3b C ++

→ Keine Nachresektion, außer
bei verbliebenem mammographischem Korrelat

* TDLU = terminale ductulolobuläre Einheit

Papillom

- Umfasst: 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 (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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➤ **Solitäres Papillom ohne Atypien in Stanz-/Vakuumbiopsie**

→ keine weiteren Maßnahmen, wenn Biopsie ausreichend repräsentativ (100mm²) und keine Diskordanz zur Bildgebung

3a C ++

➤ **Atypisches Papillom in Stanz- / Vakuumbiopsie:**

→ Offene Biopsie

3a C ++

➤ **Papillom am Rand von Resektaten:**

→ Keine verfügbaren Daten

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)

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➤ 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:

→ Keine Nachresektion

3b C ++

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

**Oxford / AGO
LoE / GR**

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 ++**

Prävention bei Läsionen mit unsicherem biologischem Potential

**Oxford / AGO
LoE / GR**

- **Tamoxifen für Frauen > 35 Jahre – Reduktion von DCIS und invasivem Karzinom** **1a A +**
- **Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen** **1b A +/-**
- **Raloxifen für postmenopausale Frauen – Reduktion nur von invasivem Karzinom** **1b A +/-***

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.

***Risk situation as defined in NSABP P1-trial (1,66% in 5 years)**

Prävention bei Läsionen mit unsicherem biologischem Potential (Tamoxifen)

NSABP-P1 Study, update 2005

	Hormontherapie Rate/ 100WE	Tamoxifen Rate/ 100WE	RR	95%-CI
Alle Frauen	629	359	0.57	0.46-0.70
Mit/dne LGS	593	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%	11.93	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 (Gail $\geq 1,66\%$):

- mit LIN , mit ADH
- mit genetischer Belastung

Sollte Frauen nicht angeboten werden:

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

Prävention bei Läsionen mit unsicherem biologischem Potential (Tamoxifen) - NW

**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.

Prävention bei Läsionen mit unsicherem biologischem Potential (Raloxifen)

NSABP-P2 Study, STAR trial 2006

	Tamoxifen : Rate / 1000 WE	Raloxifen Rate / 1000 WE	RR	95% CI
Alle Frauen	4.30	4.41	1.02	0.82-1.28
Mit/ohne LIN	3.76	3.89	1.03	0.81-1.33
mit LIN	9.83	9.61	0.98	0.58-1.63
Mit/ohne ADH	4.06	4.03	0.99	0.76-1.28
mit ADH	5.21	5.81	1.12	0.72-1.74

Angebote nur für Frauen mit erhöhtem Brustkrebsrisiko:

- ≥ 35 J. Gail 1,66% oder postmenopausal

Sollte Frauen nicht angeboten werden:

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

Prävention bei Läsionen mit unsicherem biologischem Potential (Aromatasehemmer)

Einschlußkriterien:

Results for prior ALH,
ADH, LCIS (HR AI vs Plac):

➤ IBIS.2:

- | | |
|---------------------------|------------------------------|
| ➤ Zuvor ADH, ALH, or LCIS | ➤ Ja (7J-MaCa-Risiko 12,1%): |
| Anastrozol: 154 (8.0%); | HR 0,31 (0,12–0,84) |
| Placebo: 190 (9.7%) | ➤ No (7J-MCa-Risiko 4,9%): |
| | HR 0,52 (0,31–0,78) |

➤ MAP.3:

- | | |
|----------------------------|----------------------------|
| ➤ Zuvor ADH, ALH, or LCIS: | ➤ Yes: HR=0,61 (0,20–1,82) |
| Exemestan: 185 (8.1%); | ➤ No HR=0,26 (0,11–0,64) |
| Placebo: 188 (8.3%) | |

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 2003–2014:**
**Audretsch / Brunnert / Costa / Fersis /
Friedrich / Hanf / Junkermann / Lux
/Maass / Möbus / Nitz / Oberhoff / Scharl /
Solomayer / Souchon / Thill / Thomssen**
- **Version 2015:**
Blohmer / Nitz

Prätherapeutische Abklärung suspekter Läsionen (BIRADS 4)

Oxford / AGO
LOE / GR

➤ 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%), Multizentrität und ein Lokalrezidiv.

DCIS - Prognosefaktoren für lokales und lokoregionäres Rezidiv

Oxford / AGO LOE / GR

➤ 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	2b	C	+/-
➤ DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom	3b	C	++
➤ Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)	2b	C	-

DCIS Radiotherapie

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Radiotherapie nach:

- **Brusterhaltender Operation (BEO) (gesamte Brust, WBI)**
- **Mastektomie**

**Oxford / AGO
LOE / GR**

1a	A	+
2b	B	--

Sonderformen der Radiotherapie:

- **Teilbrustbestrahlung**
- **Hypofraktionierte Radiotherapie**
- **Boost-RT des Tumorbettes**
 - **Bei Patientinnen unter 45-50 Jahren**

3a	D	--
2b	D	+/-*
2b	D	--
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):
< 2,5 cm, low and intermediate nuclear grade, mammographisch entdeckt

* hierzu liegen noch keine ausreichenden Daten zur Lokalrezidivrate vor

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

Adjuvante Systemtherapie

Oxford / AGO
LOE / GR

➤ 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 --

Zur Prävention der Gegenseite nach Mastektomie siehe Kapitel zur Prävention

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.**

**Staley H, McCallum I, Bruce J. Postoperative Tamoxifen for
ductal carcinoma in situ: Cochrane systematic review and
meta-analysis. Breast. 2014 Oct;23(5):546-51. doi:
10.1016/j.breast.2014.06.015. Epub 2014 Jul 9.**

Lokalrezidiv des DCIS nach Tumorektomie

**Oxford / AGO
LOE / GR**

Nach Radiatio

- **Einfache Mastektomie
+ SN B**

3a	C	+
5	D	+
5	D	+/-

- **Sekundäre Tumorektomie
führt zu Rezidiven in bis zu 30 % der Fälle
(NSABP B17)**

Keine Radiotherapie

- **Therapieindikation wie bei primärer
Erkrankung**

3	C	++
---	---	----

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

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Operative Therapie des Mammakarzinoms unter onkologischen Aspekten

START

Operative Therapie des Mammakarzinoms unter onkologischen Aspekten

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➤ Versionen 2002–2014:

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

➤ Version 2015:

Thill / Rezai

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AGO: ++

Die operative Therapie ist nur einer von mehreren Teilschritten bei der Behandlung des Mammakarzinoms. Daher ist sowohl eine diagnostische als auch eine onkologische Expertise unumgänglich und definitive Voraussetzung.

Präoperative Diagnostik

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

- Keine signifikante 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 ++**

Nur bei hohem Risiko für Fernmetastasen und / oder Symptomen:

➤ **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

**Oxford / AGO
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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➤ Nicht palpable Läsionen

➤ Bildgebend gestützte Drahtmarkierung

2b B ++

➤ Radionuklidmarkierung

2b B +/-

➤ Präparateradiographie oder -ultraschall

2b B ++

➤ Tumorfremie Resektionsränder

(auch bei ungünstiger Biologie reicht "no cells on ink")

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) ohne neoadjuvante Therapie

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**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|------------|
| ➤ Multizentrität | 2b | B | +/- |
| ➤ Histologisch befallene Resektions-
ränder trotz wiederholter
Nachresektion | 2b | B | - - |
| ➤ Inflammatorisches MaCa | 2b | B | - - |

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**OP nach neoadjuvanter Chemotherapie siehe Kap. „Neoadjuvante
Chemotherapie“**

Axilläre Lymphknotendisektion (ALND) I

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	Oxford / AGO LoE / GR		
➤ Axilläre Lymphknotendisektion			
➤ Endpunkt: Überleben (bei adäquater, multimodaler Therapie)	3	D	-
➤ Endpunkt: Staging	3	A	++
➤ Endpunkt: Lokoregionale Tumorkontrolle	2a	A	+/-
➤ Axilläre Lymphknotendisektion bei:			
➤ DCIS	2b	B	--
➤ Wenn SLN-Exzision möglich	1a	A	--
➤ SN positiv (cT1/2 cN0*, < 3 SN+, BET + tangentialer Radiatio, adäquate Systemtherapie)	1a	B	+/-
➤ SN + (mic)	1b	A	-
➤ SN (i+)	2b	B	--
➤ SN + Mastektomie (keine Radiotherapie der Thoraxwand)	1b	B	+
➤ SN + Mastektomie (Radiotherapie der Thoraxwand)			
➤ Nur wenn T1, T2 und 1-2 pos. SLN	5	D	+/-
Axilladisektion indiziert, aber nicht möglich			
➤ Radiatio analog AMAROS-Studie	1b	B	+/-

* Studienteilnahme empfohlen

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*				2a	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	2a 2b	B B	+/- +
		ycN+ (CNB/FNA)	ALND	2b	B	++

*Technetium Kolloid + Patentblau,
Studienteilnahme

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

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Sentinel-Lymphknoten-Exzision (SNE)

Indikationen I

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	Oxford / AGO LoE / GR		
➤ Klinisch (cN0) / sonographisch neg. Axilla	1b	A	++
➤ Zusätzliche FNA / Stanzbiopsie (klinisch/sonographisch suspekter axillärer Lymphknoten) (plus Clipmarkierung bei neoadjuvans), um eine SNE zu ermöglichen	2a	B	+
➤ 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

Oxford / AGO LoE / GR

- Während Schwangerschaft oder Stillzeit (nur Tc, 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

Sentinel-Lymphknoten-Exzision

Markierung

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➤ ^{99m}Tc Kolloid	1a	A	++
➤ Patentblau	1a	B	+/-
➤ Methylenblau	2b	B	-
➤ Indocyaningrün (ICG)*	2b	B	+/-
➤ SPIO*	2b	B	+/-

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***SPIO: Superparamagnetic Iron Oxide**

*** Studienteilnahme**

Operatives Vorgehen nach Neoadjuvanter Therapie

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➤ Rechtzeitige Clip-Markierung des Tumors	5	D	++
➤ Operation	2b	C	++
➤ Freie Resektionsränder	5	D	++
➤ Exzision in neuen Tumorgrenzen	3b	C	+

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	++
➤ TAM gleichzeitig mit Radiotherapie	3b C	+
➤ AI gleichzeitig mit Radiotherapie	3b C	+

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Onkoplastische und rekonstruktive Mammachirurgie

Plastisch-rekonstruktive Aspekte nach Mastektomie

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

- **Version 2015:**
Bauerfeind / Brunnert

Definition der onkoplastischen Operation

Der Einsatz plastischer chirurgischer Techniken zum Zeitpunkt der Tumorentfernung, um sichere Resektionsgrenzen zu erreichen und eine ästhetische Brustform zu ermöglichen. Onkoplastische Techniken reduzieren die Anzahl von Re-exzisionen, erhöhen die Anzahl von Brust erhaltenden Operationen und führen zu hoher Patientenzufriedenheit.

Onkoplastische brusterhaltende Operation

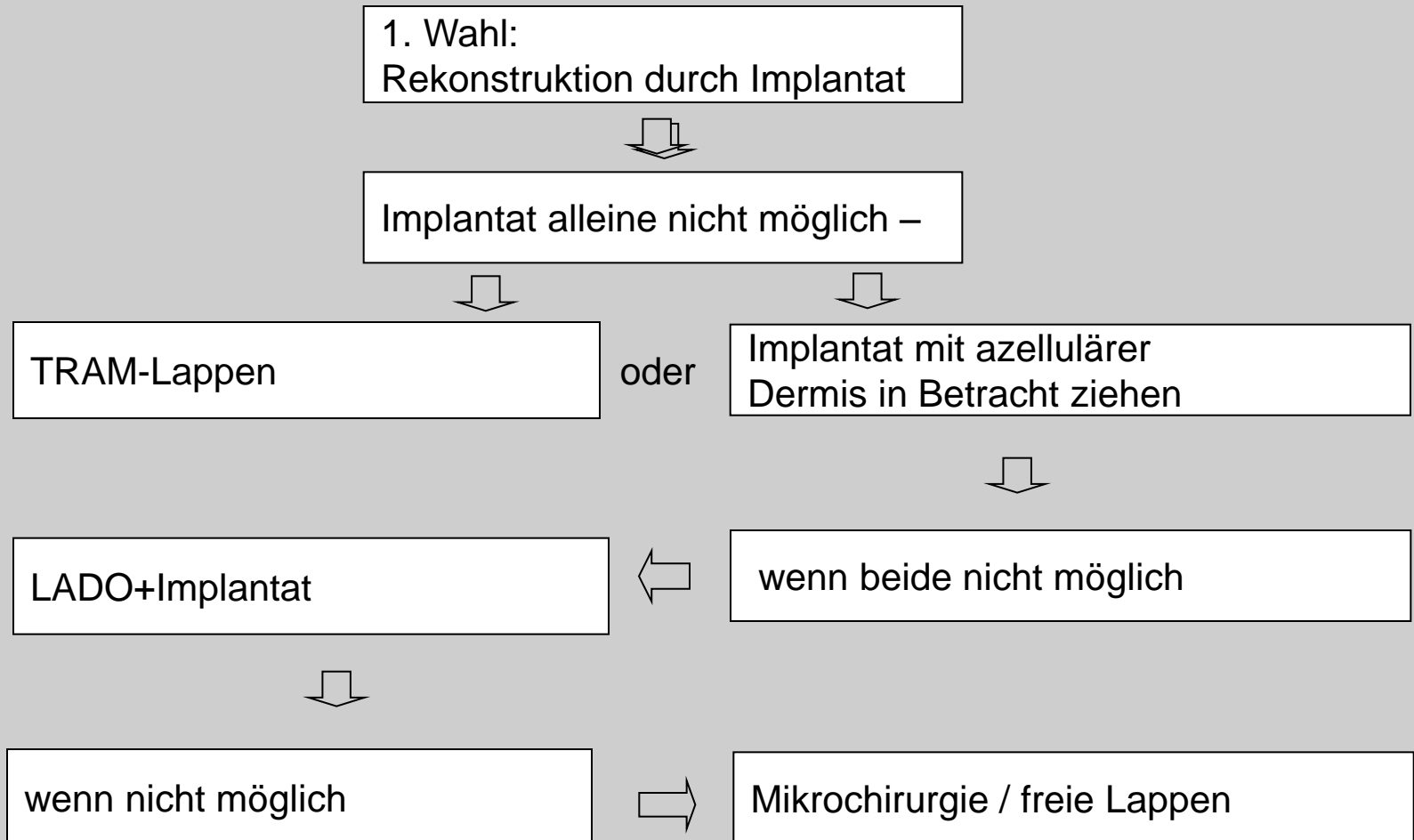
Oxford / AGO
LoE / GR

- | | | | |
|---|-----------|----------|----------|
| ➤ Tumoradaptierte Reduktionsplastik | 2a | B | + |
| ➤ Mastopexie | 3a | B | + |
| ➤ Onkoplastische Verschiebetechniken | 2a | B | + |
| ➤ Partielle Mastektomie mit Gewebstransfer | 3b | B | + |

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Algorithmus der Brustrekonstruktion



Möglichkeiten der Rekonstruktion nach Mastektomie

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	Oxford / AGO LoE / GR		
➤ Einsatz von mit Silikongel gefüllten Implantaten	2a	B	+
➤ Autologer Gewebetransfer	2a	B	+
➤ Gestielter Gewebetransfer	2a	B	+
➤ Freier Gewebetransfer (mit Gefäßanastomosen)	2a	B	+
➤ Autologer Gewebetransfer kombiniert mit Implantaten	3a	C	+

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Cave: BMI >30, Raucher, Diabetes, Strahlentherapie, Alter

Zeitpunkt der Rekonstruktion

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LoE / GR

➤ Intervallrekonstruktion

3b B ++

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

➤ Sofortrekonstruktion

3b B ++

- Obligat bei SSM/NSM
- Vermeiden des Postmastektomie-Syndroms

➤ Verzögerte Sofortrekonstruktion

(„Delayed-immediate BR“)

3b B +/-

Zeitpunkt der Rekonstruktion mit Implantaten nach MX

Oxford / AGO LoE / GR

➤ Implantat-Rekonstruktion (IR)

- IR ohne Strahlentherapie (RT)
- IR nach MX und RT
- IR vor RT / nach PBRT
 - Cave: hohe Komplikationsrate
- IR nach sekundärer MX (nach BET)
- Perioperativ verlängerte Antibiose
(mindestens 48 Stunden)

2a	B	+
2a	B	++
2b	B	+/-
2a	B	+
2a	B	+/-
3b	C	+

Techniken Gewebe zu ersetzen

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- **Eigengewebe (z.B. Lado*)**
- **Azelluläre Dermis (ADM)**
- **Synthetische Netze**

Oxford / AGO LoE / GR

3b	C	+#
2b	B	+#
2b	B	+#

* Latissimus dorsi Lappen

Teilnahme an Registerstudien empfohlen

Lipotransfer

Oxford / AGO LoE / GR

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

Gestielte Lappen zur Rekonstruktion

**Oxford / AGO
LoE / GR**

Brustrekonstruktion (BR) mit autologem Gewebe

- TRAM, Latissimus-dorsi-Lappen (können muskelsparend präpariert werden)
- Delayed-TRAM bei Risikopatientinnen
- Ipsilateral gestielter TRAM
- Radiotherapie:
 - BR nach RT
 - BR vor RT

3b C +

3a B +

3b A +

2a B +

2a B +/-

**(erhöhte Rate an Fibrosen,
Wundheilungsstörungen, Liponekrosen)**

Freie Lappen zur Rekonstruktion

Oxford / AGO
LoE / GR

Freier Gewebetransfer

- Freier TRAM
- DIEP
- SIEA
- SGAP- / IGAP
- Free gracilis flap (TMG)

3a	B	+/-
3a	B	+
3a	C	+/-
4	C	+/-
4	C	+/-

Vorteil:

- Freier TRAM und DIEP sind potenziell muskelsparend. DIEP hat niedrige Rate an Hernien.

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

Oxford / AGO
LoE / GR

- **Muskelsparende Techniken und sorgfältiger Verschluss der Bauchdecke führen zu niedrigen Komplikationsraten unabhängig von der verwendeten Methode**
- **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**

3a A ++

Lappen-Implantat-Kombination

**Oxford / AGO
LoE / GR**

Lappen-Implantat-Kombination

LDF + Implantat

- Nach RT
- Vor RT

2b	C	+
3b	C	+
5	D	-

Vorteile:

- TRAM: bevorzugt Implantateinlage nach Intervall
- Verbesserte Abdeckung des Implantates
- Geeignet zur Rekonstruktion bestrahlten Gewebes

Nachteil:

- Muskelkontraktion (Lado)

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

Oxford / AGO
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 | + |

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

Oxford / AGO
LoE / GR

- | | | | |
|---|----|---|------|
| ➤ 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

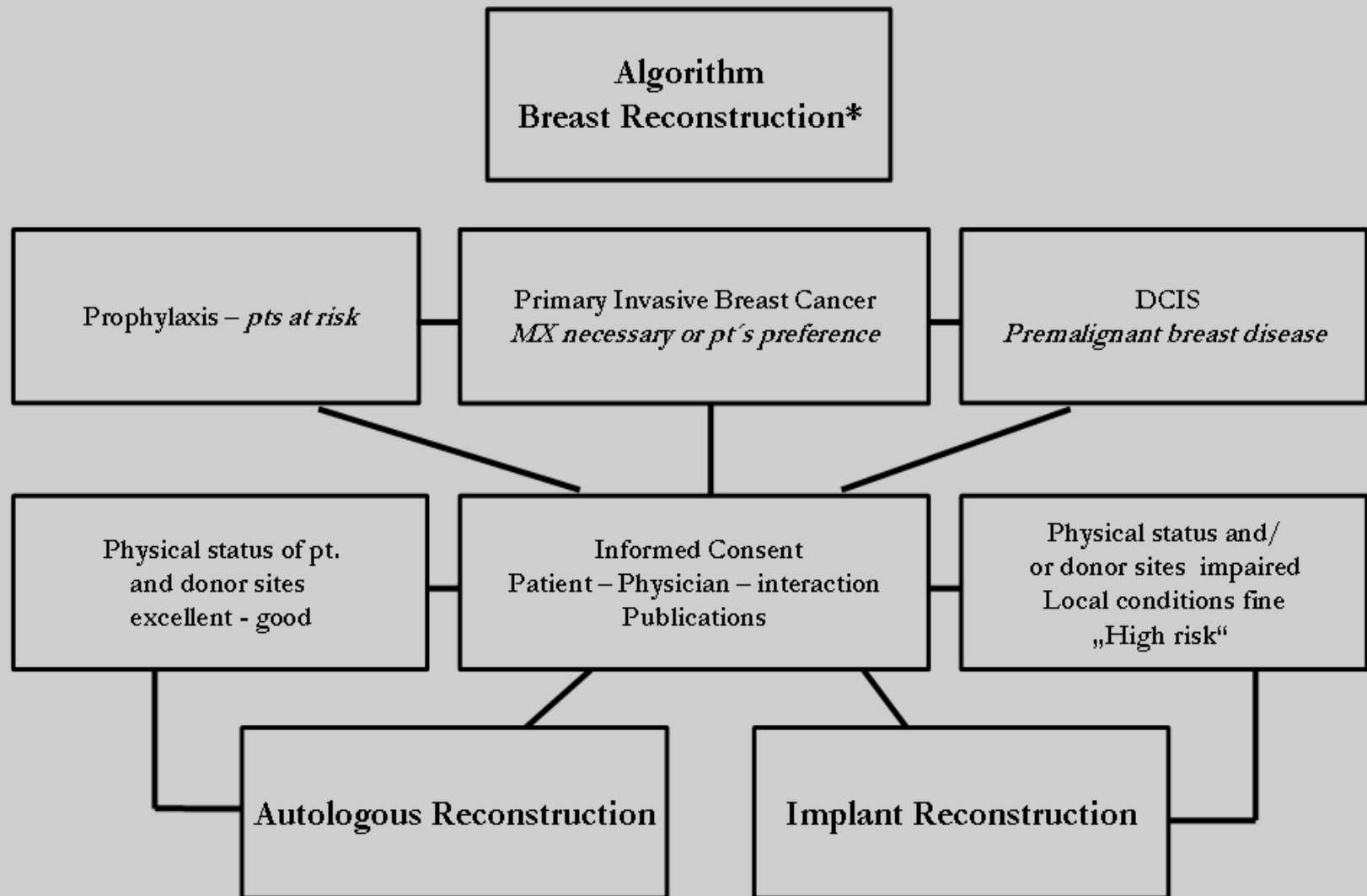
Formen der Risiko-reduzierenden bilateralen Mastektomie

**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 | +/- |

Algorithmus der Brustrekonstruktion

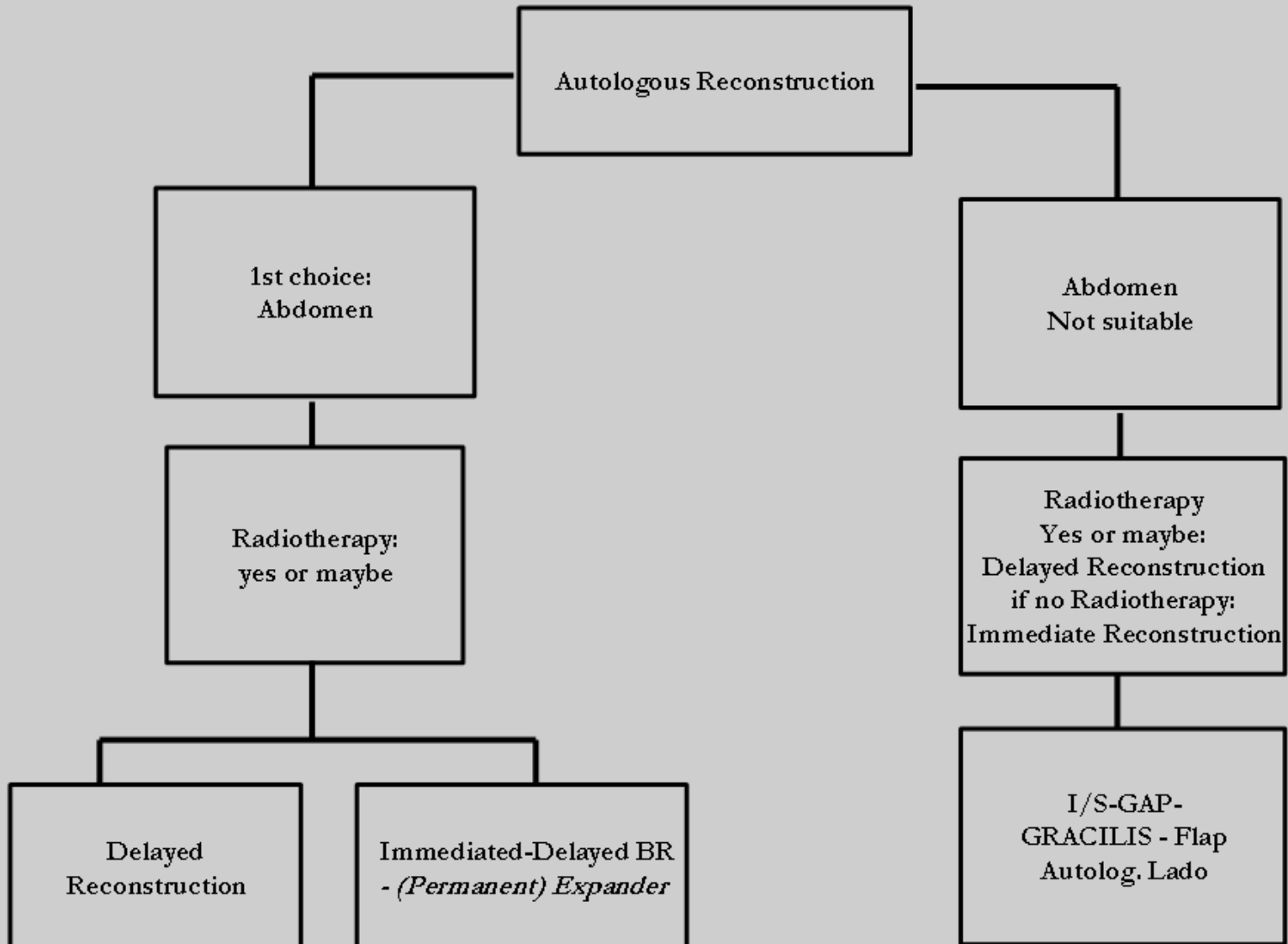


*Brunnert, K. Gyn. Prax., Band 31, 2007

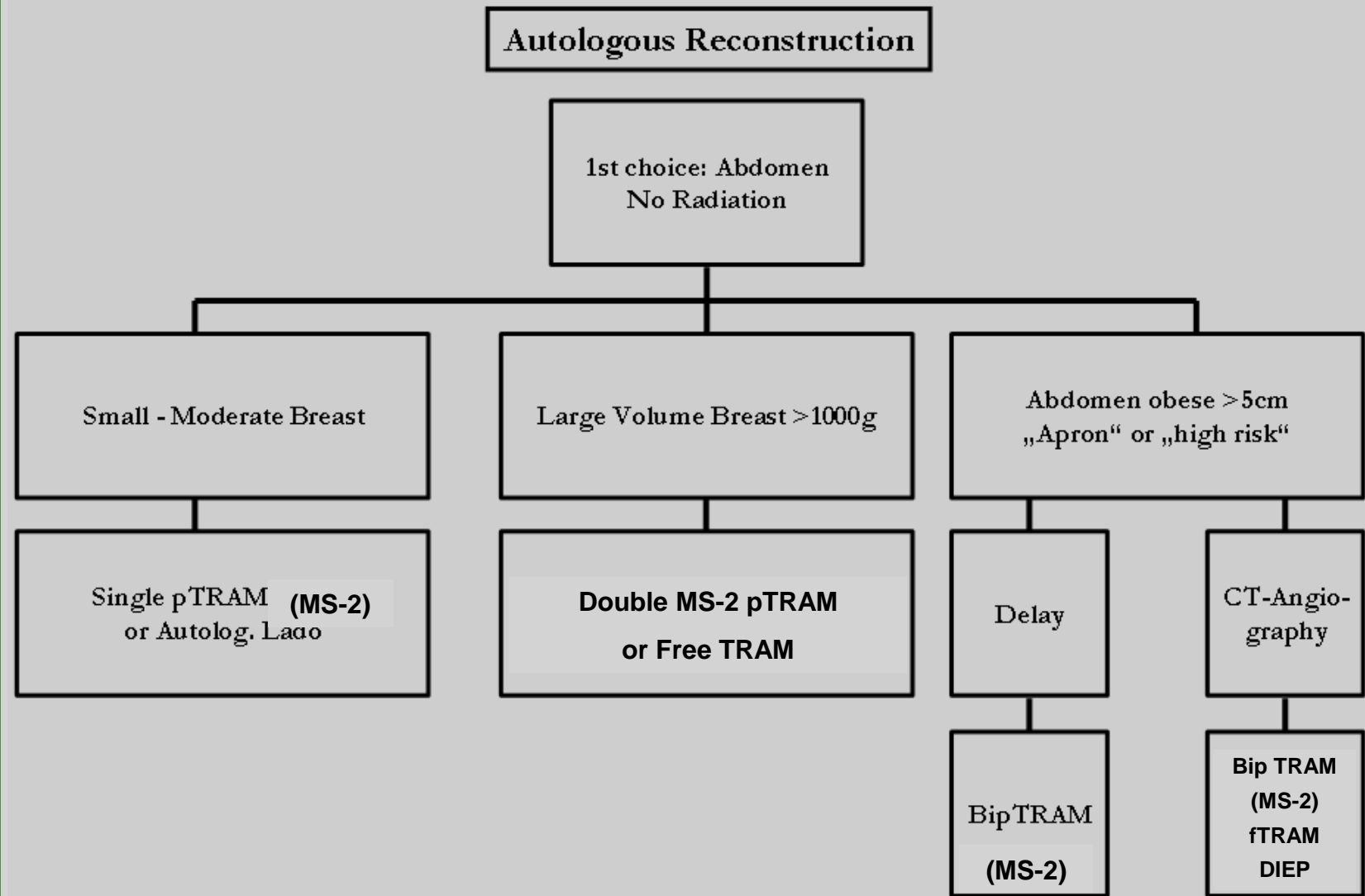
Algorithmus der autologen Brustrekonstruktion (1)

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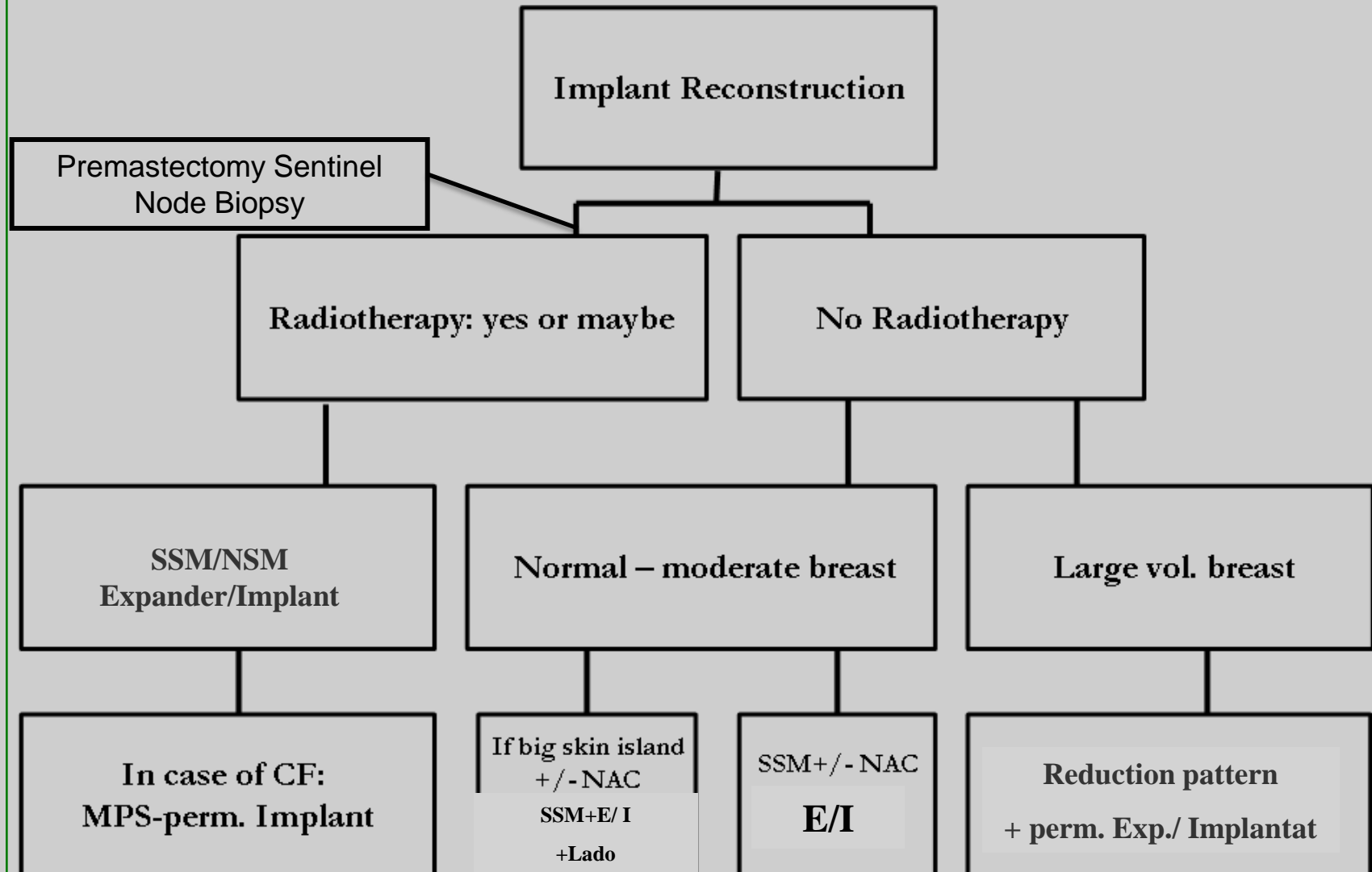
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Algorithmus der autologen Brustrekonstruktion (2)



Algorithmus der Brustrekonstruktion mit Implantat



Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

➤ Versionen 2002–2014:

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

➤ Version 2015:

Scharl / Stickeler

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** **++**

Adjuvante endokrine Therapie

Oxford / AGO
LoE / GR

Standardtherapie für rezeptorpositive Tumoren:

- **Endokrine Therapie** **1a A ++**

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

Adjuvante endokrine Therapie

Oxford / AGO
LoE / GR

- **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 ++

- **Standard Therapiedauer 5 Jahre**
- **Therapiedauer bis zu 10 Jahren nach individueller Nutzen-Risiko-Abwägung, insbes. bei erhöhtem Risiko (z.B. N+)**
- **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 postmenopausalen Pat. mit Hochrisiko- und lobulären Karzinomen**
- **Bislang keine Evidenz für AI > 5 Jahre**

Adjuvante endokrine Therapie bei prämenopausalen Patientinnen

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➤ **Tamoxifen* 5-10 Jahre**

1a A ++

➤ **GnRHa Monotherapie**

1a B +

(nur bei relevanten Kontraindikationen für Tam)

Bei Pat. mit Ovarialfunktion (innerhalb v 8 Monaten) nach adjuvanter CHT (Explorative retrospektive Analyse weist auf größeren Benefit bei jungem Alter hin):**

➤ **#OFS (Ovarialfunktionssuppression) 5 J. + TAM 5 J.**

1b B +/-

➤ **#OFS 5 J. + AI 5 J.**

1b B +/-

OFS (Ovarialfunktionssuppression)

* **Behandlung so lange tolerabel and prämenopausal**

* **Switch zum AI optional wenn Patient. postmenopausal wird**

gesteigerte Nebenwirkungen können Compliance beeinträchtigen. Höhere Compliance bei TAM ist effektiver als Kombination mit GnRH oder Behandlung mit GnRH+AI mit eingeschränkter Compliance.

** **Behandlungsdauer kann auf bis zu 10 Jahre Tam verlängert werden**

Adjuvante endokrine Therapie bei prämenopausalen Patientinnen

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➤ 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	+

Adjuvante endokrine Therapie bei postmenopausalen Patientinnen

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➤ AI für 5 J.

- Präferenz bei lobulären Karzinomen
- Sequential therapy for 5 -10 yrs.
- Tam → AI (2-5 yrs.)*
- AI (2-5 yrs.)* → Tam
(Präferenz bei N+ Status)

➤ Tamoxifen 20 mg/d für 5-10 J.

* Dauer der AI Therapie \leq 5 J.

1a	A	+
2b	B	++
		++
1a	A	
1b	C	
1a	A	++

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

Oxford / AGO
LoE / GR

Prävention der Ovarialfunktion

CHT + GnRHa

1b B +/-

(GnRHa Applikation > 2 Wochen vor Chemotherapie)

Beeinflussung des Chemoeffektes nicht ausgeschlossen!

- Beratung über Fertilitätserhaltung 4 C +
- Fertilitätserhalt mit assist. reprod. Therapie 4 C +

Testung der ovariellen Reserve

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Einschätzung der ovariellen Reserve bei infertilen Patientinnen (>6-12 Monate ohne Konzeption)*

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5 C +

Tests zur Fertilitäts-Beurteilung

- | | | | |
|----------------------------------|-----------|----------|------------|
| ➤ Anti-Müller Faktor | 3b | B | +/- |
| ➤ Antrale Follikelzählung | 3b | B | +/- |

* Tests werden vorgeschlagen für Frauen > 35 J und Infertilität für 6-12 Monate; die Tests präzisieren nicht den Misserfolg einer Konzeption, aber helfen über das potentiell verkürzte Zeitfenster für eine erfolgreiche Konzeption aufzuklären und über die Möglichkeiten einer Infertilitätsbehandlungen aufzuklären.

Kontrazeptive Möglichkeiten für Frauen nach Brustkrebs

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	Oxford / AGO LoE / GR		
➤ 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

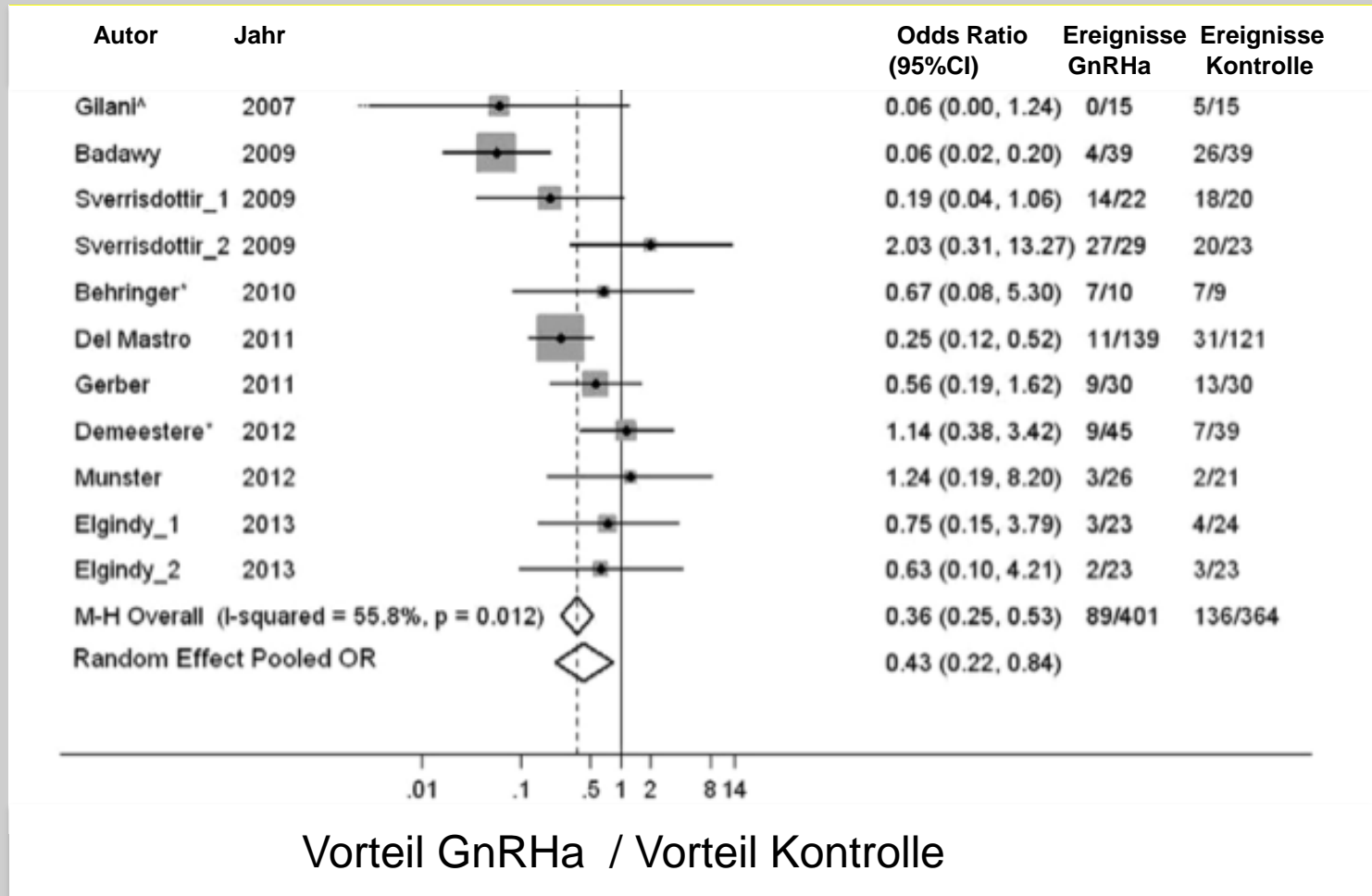
Ovarian Function Preservation – Comparison of Randomized Trials

	ZORO	PROMISE	Munster et al. - US	POEMS
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years
Treatment	goserelin	triptorelin	triptorelin	goserelin
Start of treatment	>2 weeks prior to cht	>1 week 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	Ovarian failure at 2 yrs 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%	
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predictive factor
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	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%
Median time to restoration of menses (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	n.d.
Cyclophosph. dose	4600 vs. 4700mg	4080 vs. 4008 mg	n.r.	n.a.

Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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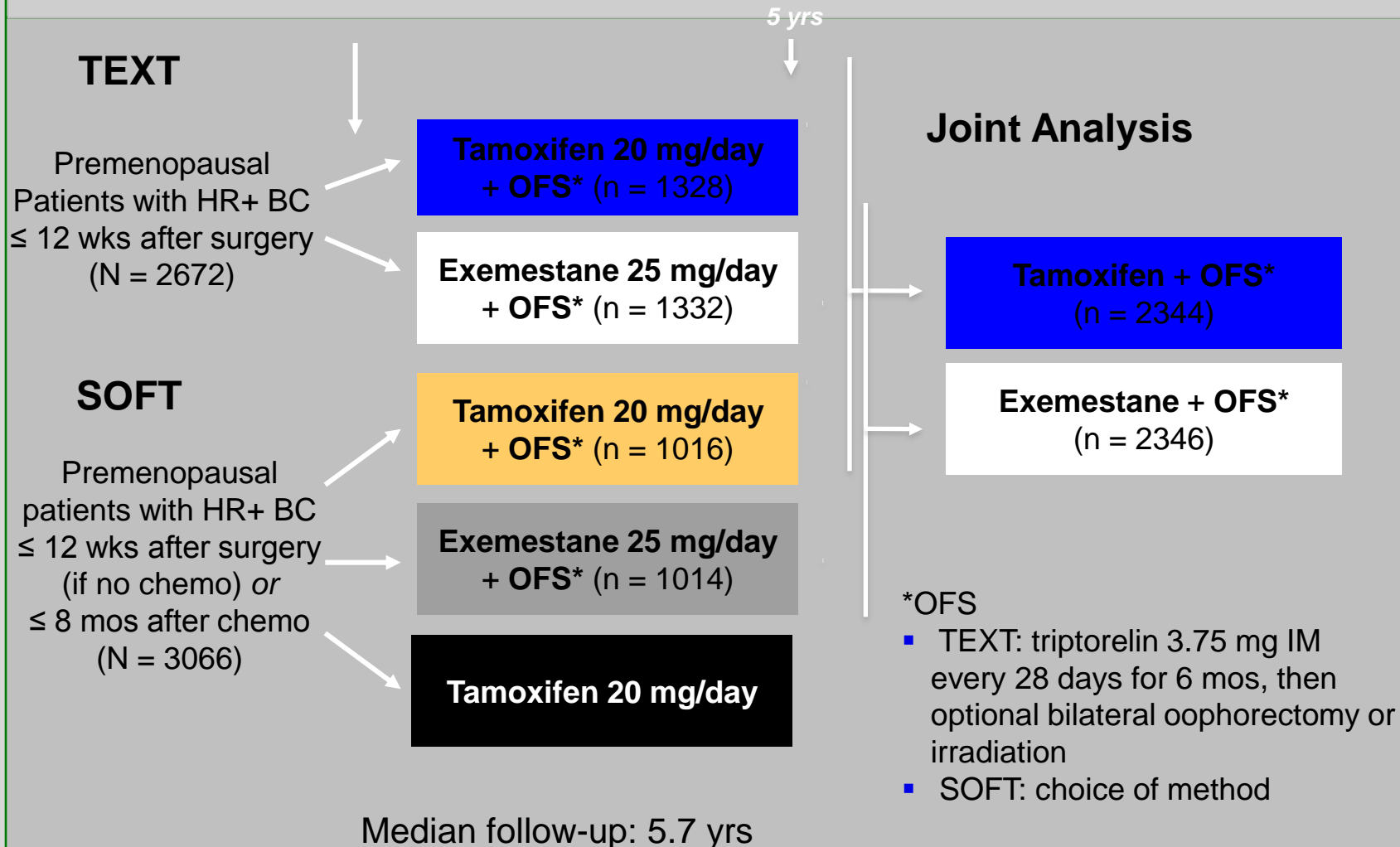
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TEXT /SOFT Joint Analysis

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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

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.

Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserve (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268–273)

Test	Details
FSH (follicle stimulating hormone) plus estradiol	<ul style="list-style-type: none"> • Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation
Anti Müllerian Hormone (AMH)	<ul style="list-style-type: none"> • No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation
Antral follicle count (AFC)	<ul style="list-style-type: none"> • Number of visible follicles (2–10 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.

10 yrs versus 5 yrs Breast Cancer Mortality in ER+

Rate ratio per period in aTTom and ATLAS

5 yrs. vs. 10 yrs Tamoxifen

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	10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)	10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)	10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) p = 0.07	0.75 (0.63-0.90) p = 0.002	0.75 (0.65-0.86) p = 0.00004
All years	0.88 (0.74-1.03) p = 0.1	0.83 (0.73-0.86) p = 0.004	0.85 (0.77-0.94) P= 0.001

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**FORSCHEN
LEHREN
HEILEN**

nach Grey et al ASCO 2013
J Clin Oncol 31, 2013 (suppl. Abstr 5)

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Adjuvante zytostatische und zielgerichtete Therapien

START

Adjuvante zytostatische und zielgerichtete Therapien

- **Version 2002:**
Möbus / Nitz
- **Versionen 2003–2014:**
Harbeck / Jackisch / Janni / Loibl/ von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Solomeyer/ Stickeler / Thomssen / Untch
- **Version 2015:**
Schütz / Lux

Subtyp-spezifische Strategien zur Systemtherapie

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- **Wenn die Indikation zur Chemotherapie aufgrund der Tumorbiologie gegeben ist, sollte eine neoadjuvante Therapie erwogen werden** **++**
- **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** **+**

Adjuvante Chemotherapie ohne Trastuzumab: Überblick

**Oxford / AGO
LoE / GR**

- **Anthrazyklin-/ taxan-basierte Chemotherapie**

1a A ++
- **Wenn Anthrazykline nicht gegeben werden können**
 - **Docetaxel plus Cyclophosphamid**

1b B +
 - **Paclitaxel mono wöchentlich**

1b B +/-
 - **CMF**

1a A +/-
- **Dosis-dichte Therapie bei hoher Tumorlast**

1a A ++

Empfohlene Regime für die adjuvante Chemotherapie

Oxford / AGO
LoE / GR

Anthrazyklin-/ taxan-basierte Regime

➤ EC → P _w	E ₉₀ C q3w x 4 → P ₈₀ qw1 x 12	1b ^a	B	++
➤ DAC	D ₇₅ A ₅₀ C q3w x 6	1b	A	++
➤ AC → P _w	A ₆₀ Cq 3w x 4 → P ₈₀ qw1 x 12	1b	A	++
➤ AC → D	A ₆₀ C q3w x 4 → D ₁₀₀ qw3 x 4	1b	A	++
➤ EC → D	E ₉₀ C q3w x 4 → D ₁₀₀ qw3 x 4	1b ^a	B	++

Anthrazyklin-freie Regime

➤ DC	D ₇₅ C ₆₀₀ x 4	1b	B	+
➤ Pac mono	P ₈₀ q1w x 12	1b	B	+/-
➤ CMF	C ₆₀₀ M ₄₀ F ₆₀₀ q3w x 6	1a	A	+/-

Dosis-dichte und/ oder dosis-eskalierte adjuvante Chemotherapie bei hoher Tumorlast

Oxford / AGO
LoE / GR

Dose-dichte Regime

➤ AC q3w / Pac q1w x 12	1b	A	++
➤ *EC q3w Pac q1w x 12	1b	B	++
➤ EC q3w / Pac q2w	1b ^a	A	+
➤ EC q2w / Pac q1w	1b	B	+
➤ ACPac / AC-Pac q2w	1b	A	+

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

➤ E-Pac-C q2w	1b	A	++
---------------	----	---	----

* Extrapoliert von Doxorubicin-Studien

Adjuvante Chemotherapie: weitere Therapien

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------------------|----------|------------|
| ➤ Capecitabin-haltige Therapie bei TNBC | 1a | B | +/- |
| ➤ Platin-haltige Therapie bei TNBC | 5 | D | +/- |
| ➤ Hinzunahme von 5-Fluorouracil zu EC/AC | 1b^a | A | - - |

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Adjuvante Therapie mit Trastuzumab I

Oxford / AGO
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**
- **Sequentiell bis zu 3 Monaten nach Chemotherapie**

1a A ++

1b B +

Dauer

- **Für 1 Jahre**
- **Für 2 Jahre**
- **Für 0,5 Jahre**

1b A ++

1b A -

1b A +/-

Trastuzumab Adjuvant

Überwachung hinsichtlich CHF

Oxford LoE: 5

GR: D

AGO: ++

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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 weiteren zielgerichteten Substanzen

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	Oxford / AGO LoE / GR		
➤ Lapatinib	5	D	-
➤ (verzögerte adjuvante Therapie)	1b	B	-
➤ Lapatinib + Trastuzumab	1b^a	B	-
➤ Pertuzumab	5	D	-
➤ Bevacizumab	1b^a	B	--

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Neoadjuvante (Primäre) systemische Therapie

START

Neoadjuvante systemische Therapie

- **Version 2002:**
Costa
- **Versionen 2003–2014:**
**Bauerfeind / Blohmer / Dall / Fersis / Göhring
/ Harbeck / Heinrich / Huober / Jackisch /
Kaufmann / Loibl / Lux / von Minckwitz /
Müller / Nitz / Schneeweiss / Schütz /
Solomayer / Untch**
- **Version 2015:**
Friedrich / Schneeweiss

Allgemeine Überlegungen zur Systemtherapie in Abhängigkeit von Subtyp

AGO

- Bei bestehender Indikation zur Chemotherapie sollte unbedingt die Möglichkeit der neoadjuvanten Chemotherapie erwogen werden. ++
- 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
 - Plus Carboplatin bei familiärer BC/OC Belastung oder gBRCA Mutation +

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

	Oxford / AGO LoE / GR		
➤ Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie	1a	A	
➤ Pathologische Komplettremission ist mit einem besseren Überleben assoziiert, besonders in Subgruppen	1b	A	
➤ Kann Operabilität bei primär inoperablen Tumoren erreichen	1b	A	++
➤ Verbessert die Optionen für eine brusterhaltende Operation	1b	A	++
➤ Erlaubt Individualisierung der Therapie nach dem Interims-Ansprechen	1b	B	+*
➤ Erlaubt Individualisierung des post-neoadjuvanten Managements entsprechend des Risikoassassments nach neoadjuvanter Behandlung und Operation	2b	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	+

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	I	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**

1a A +

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

1b B +*

- **Platinsalze beim TNBC**

1a A +/-

- **Bei familiärer Belastung bzgl BC/OC oder BRCA Mutation**

2b B +

Mögliche carboplatinhaltige Regime in der neoadjuvanten Situation

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Author	Study	Regimen	pCR rate
Sikov WM, et al. (JCO 2015)	CALGB 40603 Phase II	Paclitaxel 80mg/m ² qw x12 + Carboplatin AUC 6 q3w x4 – dd AC q2w x4	TNBC ± Cb: 54% vs 41% (ypT0/is ypN0)
von Minckwitz G, et al. (Lancet Oncol 2014)	Gepar Sixto Phase II	NPLD 20mg/m ² qw x18 + Paclitaxel 80mg/m ² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15mg/kg q3w x6	TNBC ± Cb: 53% vs. 37% (ypT0 ypN0)
Ando M, et al. (BCRT 2014)	Phase II	Paclitaxel 80mg/m ² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4	TNBC ± Cb: 61% vs. 26%

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)	2b	B	+/-
➤ 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	1a	B	-
➤ Lapatinib + Trastuzumab in Kombination mit Chemotherapie	1a	B	+/-
➤ Pertuzumab + Trastuzumab in Kombination mit Chemotherapie	1a	B	+
➤ Zwei gegen HER2 gerichtete Substanzen ohne Chemotherapie	2b	B	+/
➤ gegen Anti-HER2 gerichtete Substanzen in Kombination mit endokriner Therapie	2b	C	+/-

* Studienteilnahme empfohlen

Neoadjuvante zielgerichtete Therapie bei HER2-negativen Tumoren

**Oxford / AGO
LoE / GR**

Chemotherapie in Kombination mit Bevacizumab

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

1b B -

1b B +/-

Neoadjuvante systemische Therapie

Vorgehen bei einem frühen Ansprechen

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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

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	2a	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 AC0ZOG	ycN0	ALND	3	B	+/-
cN0	pN+(sn) nicht analog AC0ZOG	ycN0	ALND	2b	B	+
cN+	cN+ (CNB/FNA)	ycN0	SNB ALND	2a 2b	B B	+/- +
		ycN+ (CNB/FNA)	ALND	2b	B	++

Neoadjuvante systemische Therapie

Indikationen für Mastektomie

**Oxford / AGO
LoE / GR**

- **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** 2b C +/-
 - **cT4a-c Mammakarzinom** 2b B +/-

Neoadjuvante systemische Therapie

Zeitablauf von Operation und Radiotherapie

Oxford / AGO
LoE / GR

Operation

4 C ++

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

Radiotherapie nach Operation

2b B ++

- 2–3 Wochen nach Operation

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

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➤ 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
- Aromataseinhibitoren (für > 3 Monate)
- Aromataseinhibitor + Lapatinib (HER2+)

➤ Prämenopausale Patientinnen

- mit endokrin sensiblen Mammakarzinom, die inoperabel sind und keine Chemotherapie möchten / haben können
- Tamoxifen
- Aromataseinhibitoren + LHRH

➤ Simultane chemo-endokrine Therapie

- Prognostische Faktoren während/nach NST: Quantitative ER-Expression, Expression von Ki-67, N-Status, T-Status (PEPI)

Oxford / AGO LoE / GR

2a	B	+
1b	A	+
1a ^a	B	+
2b	B	+/-
5	C	+
2b	C	+
1b	C	+/-
1b	A	-
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

◀◀ START

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Adjuvante Radiotherapie (RT)

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- **Versionen 2002 – 2014:**
**Souchon / Blohmer / Friedrichs / Göhring /
Janni / Möbus / Seegenschmiedt**

- **Version 2015:**
**Thomssen / Kühn / Untch / Scharl
Budach / Wenz / Souchon**

Vorbemerkung

- **Diese Empfehlungen zur adjuvanten Strahlentherapie bei Brustkrebs basieren auf einer Konsensdiskussion zwischen Experten der Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) und der Deutschen Gesellschaft für Radioonkologie (DEGRO)**
- **Für technische Details zur Durchführung der Strahlentherapie verweisen wir auf die entsprechenden aktualisierten Leitlinien der DEGRO 2014**
- **Für einzelne Statements konnte kein Konsens erreicht werden, die Einschätzung der DEGRO wurde jeweils in blauer Farbe wiedergegeben**

Radiotherapie (RT) nach brusterhaltenden Operationen (BEO; invasive Karzinome): - Bestrahlung der Brust -

LoE 1b B

AGO ++

< 40 Jahre	Konventionelle RT (25-28 Fraktionen) mit integriertem oder sequentielltem Boost
40 – 65 J.	Konv. RT mit integriertem oder sequentielltem Boost, oder hypofraktionierte RT mit sequentielltem Boost
> 65 Jahre	Niedriges Risiko: hypofraktionierte RT ohne Boost erwägen (15-16 Fraktionen) Hohes Risiko: RT wie für 40-65 Jahre
Ältere Pat.	Individuelle Beratung einschließlich Verzicht auf RT je nach individuellem Risiko und geriatr. Einschätzung
Jedes Alter (Lymphabflusswege)	Bei zusätzlicher Bestrahlung der Lymphabflusswege konventionell fraktionierte RT (25-28 Fraktionen)

Studienteilnahme empfohlen

Zusätzliche Informationen hinsichtlich der Effekte der Radiotherapie der Brust (BET)

➤ Hypofraktionierung:

- Einige Effekte auf das normale Gewebe waren in einem Teil der Studien zur hypofraktionierten Strahlentherapie (15-16 Fraktionen) geringer ausgeprägt als nach einer konventionell fraktionierten Strahlentherapie (Brustschrumpfung, Teleangiektasien und Brustödem).
- Die lokoregionäre Rückfallrate war in keiner der 5 randomisierten Studien statistisch signifikant unterschiedlich. In einer von 5 Studien wurde im hypofraktionierten Arm eine geringere Rate von Fernmetastasen (HR_{DFS} 0,74; 95% CI 0,59–0,94) verbunden mit einem besserem Überleben ($HR_{OS}=0,8$; $p=0,042$) beobachtet.
(*START B: Haviland JS et al. Lancet Oncol 2013; 14: 108*)

➤ Ältere Patientinnen sollten über Folgendes beraten werden:

- Die lokale Rückfallrate wird durch eine Brustbestrahlung bei älteren Pat. mit pT1-2 (bis zu 3 cm) pN0, HR-positiven Mammakarzinomen nach brusterhaltender Operation und mit adjuvanter endokriner Therapie um absolut ca. 8% nach 10 Jahren gesenkt.
Es findet sich kein Vorteil hinsichtlich des metastasenfreien Überlebens und des Gesamtüberlebens.

Radiatio im Alter nach brusterhaltender Operation (Lebenserwartung <10 Jahre)

Oxford / AGO
LoE / GR

- **Verzicht auf Radiotherapie der Brust bei Pat. mit niedrigem Rezidivrisiko, wenn eine adjuvante endokrine Therapie (z.B. 5 J. Tamoxifen) konsequent durchgeführt wird***

AGO¹	1b	A	+
DEGRO¹	1b	C	+/-
- **Geringe Erhöhung des Lokalrezidivrisikos, aber ohne Einfluss auf Gesamtüberleben; Verminderung der Toxizität**

*** Alter ≥ 70 J., pT1, pN0, HR-pos., G1-2, HER2-negativ, Resektionsrand >1 mm**

¹Unterschiedliche Interpretation der Daten durch AGO und DEGRO

BCS $\geq 70y$ $< 4cm$ cN0 : Tamoxifen vs. Tamoxifen + RT

Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

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@10 yrs (95% C.I.)	Tamoxifen	Tamoxifen plus Radiotherapy	Hazard Ratio
Local recurrence	90% (85%-93%)	98% (96%-99%)	HR=0.18 (95% CI, 0.07 to 0.42; $P < .001$)
Mastectomy- free	96% (93% - 98%)	98% (96% - 99%)	HR=0.50 (95% CI, 0.17 to 1.48; <i>n.s.</i>)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR=1.20 (95% CI, 0.63 to 2.32; <i>n.s.</i>)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR=0.95 (95% CI, 0.77 to 1.18; <i>n.s.</i>)

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Hughes KE et al J Clin Oncol 2013; 31:2382-2387

Boost und Teilbrustbestrahlung nach BEO beim invasiven Karzinom

Oxford / AGO LoE / GR

➤ Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensbenefit)

➤ < 40 Jahre

1b B +

➤ 40 - 60 Jahre

1b B ++

➤ > 60 Jahre, G3 oder >pT1

1b B ++

2b B +/-

➤ Intraoperative Radiotherapie (IORT/IOERT)

➤ Als Boost-Bestrahlung vor Ganzbrust-RT

2a B +

➤ Als alleinige Radiotherapie-Maßnahme bei pT1 pN0 R0 G1-2, non-lob., >50 J., kein extensives DCIS, HR+)

➤ IORT während Erst-Op 50 kV

1b B +/-*

➤ IOERT während Erst-Op

1b B +/-*

➤ Postoperative Teilbrustbestrahlung als alleinige Radiotherapie-Maßnahme bei ausgewählten Pat. (ASTRO)

➤ Interstitielle Brachytherapie

1b B +/-*

➤ Intrakavitäre Ballontechnik

2b B -*

➤ APBI (IMRT) **

2b B -*

*Studienteilnahme empfohlen; keine Langzeitdaten

Boost vs no Boost: EORTC 22881-10882 Trial

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@20 yrs (95% C.I.)	Boost (n=2.661)	No boost (n=2.657)	Hazard Ratio (95% C.I.)
Overall Survival (Δ =-1.4%)	59.7% (56.3–63.0)	61.1% (57.6–64.3)	HR 1.05 (0.92–1.19) n.s.
Cumulative Risk of Ipsilateral Breast Tumour Recurrence			
All patients	12.0% (9.8–14.4)	16.4% (14.1–18.8)	HR=0.65 (0.52–0.81); p<0.0001
≤40 years (Δ =11.6%)	24.4% (14.9–33.8)	36.0% (25.8–46.2)	HR=0.56 (0.34–0.92); p=0.003
41–50 years (Δ =5.9%)	13.5% (9.5–17.5)	19.4% (14.7–24.1%)	HR=0.66 (0.45–0.98); p=0.007
51–60 years (Δ =2.96%)	10.3% (6.3–14.3)	13.2% (9.8–16.7)	HR=0.69 (0.46–1.04); p=0.020
>60 years (Δ =3.0%)	9.7% (5.0–14.4)	12.7% (7.4–18.0)	HR=0.66 (0.42–1.04); p=0.019

(Median F/U 17.2 y)

nach: Bartelink et al. Lancet Oncol 2015; 16: 47–56

Postmastektomie-Bestrahlung (PMRT)* der Thoraxwand

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- >3 positive Lymphknoten
- 1-3 positive Lymphknoten (hohes Risiko) **AGO***
- 1-3 positive Lymphknoten (niedriges Risiko*) **AGO***
- 1-3 positive Lymphknoten (jedes Risiko) **DEGRO¹**
- T3 / T4
 - pT3 pN0 R0 (ohne zusätzliche Risikofaktoren)
- R0-Resektion nicht erreichbar (bei invasiven Tumoren)
- Bei jungen Patientinnen mit hohem Rückfallrisiko
- Nach primärer systemischer Therapie (NACT):
 - RT basierend auf dem prätherapeutischen Stadium vor NACT: cN+, cT3/4a-d
 - Verzicht auf RT bei ypT0 ypN0 nach PST (NACT)**

Oxford / AGO
LoE / GR

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

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Die Indikationen zur PMRT und regionalen RT sind unabhängig von der adjuvanten systemischen Therapie

1a A

¹Unterschiedliche Interpretation der Daten durch AGO und DEGRO

* Zur Definition „niedriges Risiko“ siehe Further Information engl. Version **Studienteilnahme empfohlen

Radiotherapie der Axilla

**Oxford / AGO
LoE / GR**

- | | | | |
|--|-----------|----------|-----------|
| ➤ Tumorresiduen nach axillärer Dissektion | 5 | D | ++ |
| ➤ Sentinel-Lymphknoten negativ | 1 | B | -- |
| ➤ Axilladissektion nicht indiziert
(z.B. cN0 mit pos. SLN; s. operat. Therapie) | 2a | B | - |
| ➤ Extrakapsuläres Tumorwachstum (ECS) | 2b | B | - |
| ➤ Axilläre Mikrometastasen oder isolierte
Tumorzellen in regionalen Lymphknoten | 1b | B | -- |

Axilläre Interventionen bei Patientinnen mit positiven Sentinel-Lymphknoten

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Oxford / AGO
LoE / GR

Axilläre Dissektion oder RT der Axilla bei 1-2 pos. SLN:

- | | | | |
|--|----|---|------|
| ➤ BET und ACOSOG Z011-Kriterien erfüllt | 1b | B | +/-* |
| ➤ Keine weitere axilläre Intervention | 1b | B | +/-* |
| ➤ BET u. ACOSOG Z011-Kriterien <u>nicht</u> erfüllt | 1b | B | ++* |
| ➤ Mastektomie (ME), RT der Thoraxwand indiziert und ACOSOG Z011-Kriterien erfüllt | 5 | D | +/-* |
| ➤ Keine weitere axilläre Intervention | 5 | D | +/-* |
| ➤ ME, RT der Thoraxwand indiziert und ACOSOG Z011-Kriterien <u>nicht</u> erfüllt <i>oder</i> ME und RT der Thoraxwand <u>nicht</u> geplant | 1b | D | ++ |

Axilläre Dissektion oder RT der Axilla bei ≥ 3 pos. SLN

- | | | | |
|----------------------------|----|---|----|
| ➤ Axilläre Dissektion | 1b | B | ++ |
| ➤ Radiotherapie der Axilla | 1b | B | + |

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*Study participation recommended

Radiotherapie (RT) der übrigen lokoregionalen Lymphabflussregionen

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<u>RT der supra-/infraklavikulären Lymphregion:</u>		<u>LoE / GR / AGO</u>		
➤	≥ pN2a	1b	A	++
➤	Level III befallen	1b	A	++
➤	pN1a (hohes Risiko) AGO ¹	2b	B	+
➤	pN1a (niedriges Risiko) AGO ¹	2b	B	+/-
➤	pN1a (jedes Risiko) DEGRO ¹	2b	B	+
➤	pN0 (hohes Risiko), wenn eine RT der A. mammaria interna-Lnn. indiziert ist (s. unten)	2a	B	+/-
➤	Nach NACT/NAT (Indikationen wie für PMRT) AGO	2b	B	+/-
➤	Nach NACT/NAT bei cN+ (Ind. wie PMRT) DEGRO ¹	2b	A	+
<u>➤ RT der A. mammaria-interna-Lymphabflussregion (IMC):</u>				
➤	pN1-pN2 und HR-positiv, wenn eine adjuvante systemische Chemotherapie erfolgt ist	1b ^a	B	+
➤	pN0 high risk mit zentral/medial gelegenen Tumoren (ER+, wenn Chemotherapie erfolgt ist)	1b ^a	B	+/-
➤	IMC-RT, wenn kardiale Risikofaktoren vorliegen oder wenn Trastuzumab gegeben wird	2b	A	- -

* Zur Definition „niedriges Risiko“ siehe Further Information engl. Version

Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(median follow-up 10.9 yrs)

<u>Adjuvant treatment</u>	<u>n</u> *	<u>Hazard ratio</u> <u>(95%CI)</u>
No adjuvant reported	625	0.91 (0.59 - 1.39)
Chemotherapy	954	1.05 (0.84 - 1.32)
Endocrine therapy	1185	0.82 (0.63 - 1.06)
Both (endocrine th. and chemotherapy)	1200	0.72 (0.55 – 0.94)
Total	4004	0.88 (0.76 – 1.01)

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013

Kombination systemischer Therapien mit simultaner Radiotherapie

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- | | | | |
|---|-----------|----------|----------|
| ➤ Trastuzumab simultan zur
Radiotherapie | 2b | B | + |
| ➤ Tamoxifen simultan zur
Radiotherapie | 2b | B | + |
| ➤ AI (Letrozol) simultan zur
Radiotherapie | 2b | B | + |

***Bei HER2-positiven Tumoren sollte eine parasternale RT generell vermieden werden; keine simultane Trastuzumabtherapie bei parasternaler RT.**

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Nebenwirkungen der Therapie

Nebenwirkungen der Therapie

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- **Versionen 2004–2014:**
**Albert / Bischoff / Brunnert / Costa /
Friedrich / Friedrichs / Gerber / Göhring /
Huober / Jackisch / Lisboa / Müller / Nitz /
Schmidt / Souchon / Stickeler / Untch**

- **Version 2015:**
Lück / Dall

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

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

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ASCO SPECIAL ARTICLE

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Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn Hershman, Columbia University Medical Center, New York; Robert Dworkin, University of Rochester, Rochester, NY; Christina Lacchetti and Kate Bak, American Society of Clinical

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstriep, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi

Recommendations:

On the basis of the paucity of high-quality, consistent evidence, there are no agents recommended for the prevention of CIPN. With regard to the treatment of existing CIPN, the best available data support a moderate recommendation for treatment with duloxetine. Although the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions given the limited other CIPN treatment options. Further research on these agents is warranted.

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

Oxford / AGO
LOE / GR

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

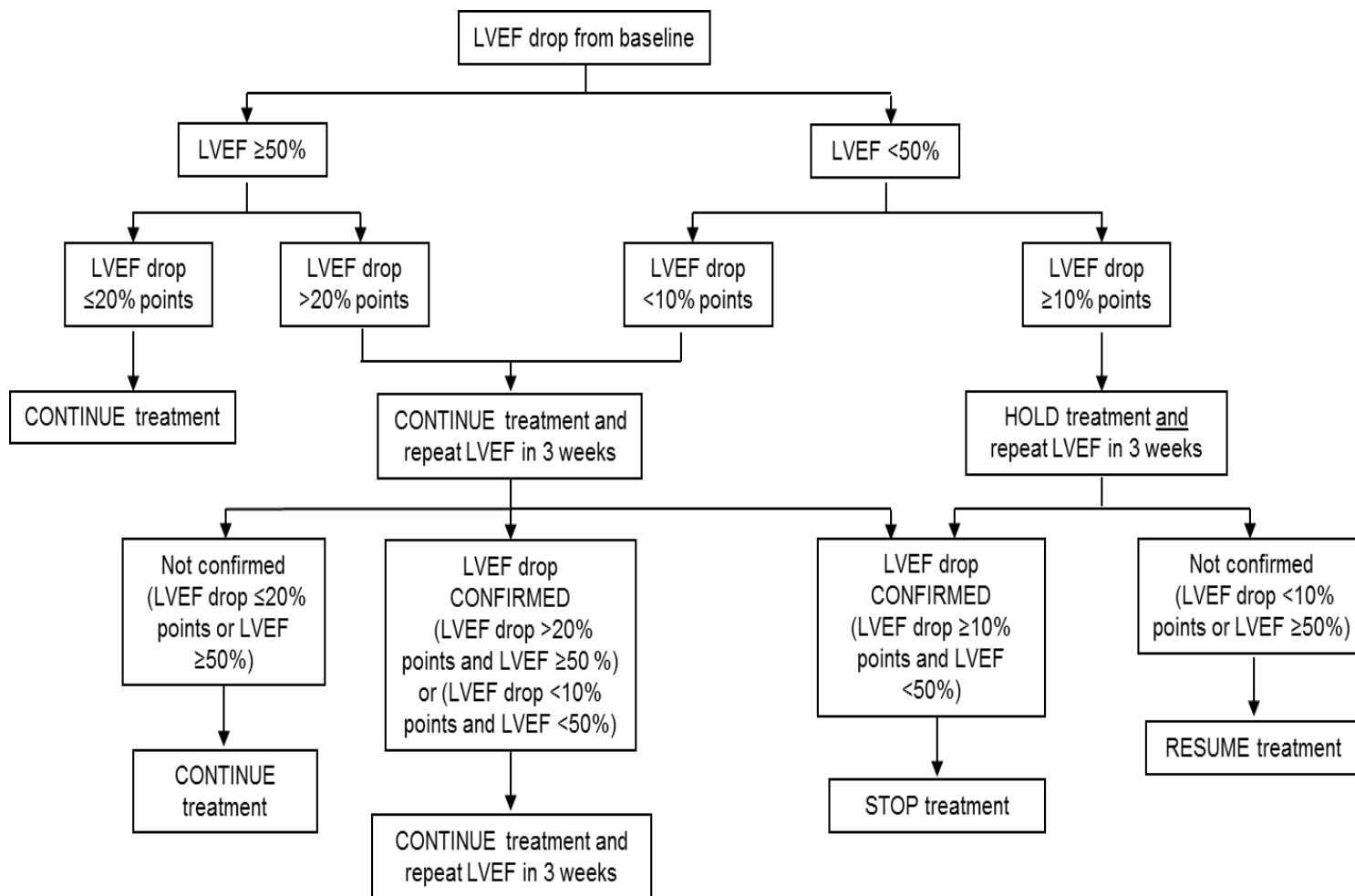
➤ Tamoxifen simultan zu Radiotherapie	3	C	+/-
➤ Chemotherapie simultan zu Radiotherapie	1b	B	-

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
- PARP-Inhibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0.5-1%
- 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

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

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 – Antikörper/ Antikörper-Effektor-Konjugate

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

Bevacizumab

- Hypertonus, linksventrikuläre Dysfunktion
Blutung, Proteinurie

1a A

Small Molecules

**Oxford / AGO
LoE / GR**

Lapatinib

- Diarrhoe, Ekzem, Fatigue

1b A

Everolimus

- Pneumonitis, Stomatitis, Hyperglykämie, Infektionen, Ekzem, Thrombozytopenie

2b B

PARP-Inhibitoren (Olaparib)

- Fatigue, Myelosuppression

3 C

cdk4/6 Inhibitoren (Palbociclip, LEE011)

- Myelosuppression, Neutropenia

3 C

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Supportive Therapie

Supportive Therapie

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➤ **Version 2002:**
Diel

➤ **Versions 2003–2014:**
**Bauerfeind / Bischoff / Costa / Dall / Diel
/ Fersis / Hanf / Heinrich / Jackisch /
von Minckwitz / Möbus / Oberhoff /
Rody / Schaller / Scharl / Schmidt /
Schütz**

➤ **Version 2015:**
Diel / Bischoff

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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 interdisziplinäre Leitlinien der AWMF:
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, angemeldet 1.7.2012, gepl. Fertigst.: 30.6.2015**

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)	1a	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	

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Praktischer Umgang mit ESF

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	Oxford / AGO LoE / GR		
	1b	A	++
➤ Epoetin α und Darbepoetin sind äquieffektiv			
➤ 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, Gilreath JA et al: Cancer- and chemotherapy-induced anemia. NCCN Clinical Practice Guidelines in Oncology 2.2015. 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**

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LoE / GR**

5 D +

1a B -

1a A ++

1a B +/-

5 D -

1a A ++

www.ago-online.de

**FORSCHEN
LEHREN
HEILEN**

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

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment

Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

FN risk $\geq 20\%$

FN risk 10-20%

FN risk $< 10\%$

Step 2: Assess factors that may increase the risk of FN:

High risk:

Age > 65 years

Increased risk:

(level I and II evidence)

Advanced disease

History of prior FN

No antibiotic prophylaxis

Other Factors:

(level III and IV evidence)

Poor performance (ECOG > 1)

Female gender

Haemoglobin < 12 g/dL

Liver, renal or cardiovascular disease

Nutritional status

Step 3: Define the patient's overall FN risk for planned chemotherapy regimen

Overall FN risk $\geq 20\%$

Overall FN risk $< 20\%$

**Prophylactic G-CSF
recommended**

**G-CSF prophylaxis not
indicated**

Reassess at
each
cycle

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

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 Eiswürfeln (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

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 $< 500 \text{ cells/mm}^3$)

- **Klinische Untersuchung**
- **Tägliche Kontrollen**
- **Hospitalisierung von Hochrisikopatienten**
- **Ambulante Therapie bei Niedrigrisikopat. möglich**
- **Differentialblutbild**
- **Blutkulturen**
- **Bildgebung der Lunge**
- **Sofortige empirische antibiot. Therapie**
- **Empirische antimykotische Therapie 4-7d bei keiner Besserung unter Antibiose**
- **GCSF als therapeutische Maßnahme**

**Oxford / AGO
LoE / GR**

5	D	++
5	D	++
1b	A	++
1b	A	+
5	D	++
5	D	++
3	C	++
1a	A	++
1b	A	++
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 | ++ |
| ➤ Bei bestehenden kardialen Risiken
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>

www.onkosupport.de

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

Supportive Therapie

Antiemetika

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

Schmerztherapie

(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie
Tumorschmerz 2014 www.dgs-praxisleitlinien.de

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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

START

Brustkrebs: Spezielle Situationen

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- **Version 2005-2014:**
**Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Harbeck / Huober / Janni / Loibl
/ Lück / Lux / Maass / Mundhenke /
Oberhoff / Rody / Scharl / Schneeweiss**
- **Version 2015:**
Solomayer / Harbeck

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	+/-
1b	B	+/-
2b	B	+
2b	C	+
2b	B	++

Brustkrebs in der Schwangerschaft*

Oxford / AGO
LOE / GR

- | | | | |
|---|---|---|-----|
| ➤ 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**
- **(Neo-)adjuvante Chemotherapie nur nach erstem Trimester (Indikation wie bei Nicht-Schwangeren)**
 - **Antrazykline: AC, EC**
 - **Taxane**
 - **MTX (e.g. CMF)**
 - **Endokrine Therapie**
- **Anti-HER2-Therapie**
- **Bisphosphonate**

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

Brustkrebs in der Schwangerschaft*

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LOE / GR

- | | | | |
|---|----|---|----|
| ➤ 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 | ++ |

* Teilnahme an Registerstudie empfohlen

Brustkrebs während Schwangerschaft / Stillperiode*: Prognose

**Oxford
LoE**

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➤ 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)

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➤ **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 (Standard Regime)**

➤ **< 70 Jahre**

1a A +

➤ **> 70 Jahre**

2a C +*

➤ **Radiotherapie**

1a A +

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

1b B +

➤ **Trastuzumab**

2b C +

** > 70 Jahre, 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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- | | | | |
|--|-----------|----------|-----------|
| ➤ 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 | 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

**Oxford / AGO
LOE / GR**

- | | | | |
|--|-----------|----------|------------|
| ➤ 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
- Hautbiopsie (mind. 2; Detektionsrate jedoch $< 75\%$)
- Präoperative Chemotherapie
 - Regime wie nicht inflammatorisches MaCa
 - Anthrazyklin- und Taxan-basiert
 - Bei HER2 + Hinzunahme von Trastuzumab
 - Bei HER2 + Hinzunahme von Trastuzumab und Pertuzumab
 - Bei HER2 + Hinzunahme von Bevacizumab
- Mastektomie nach Chemotherapie
 - Brusterhaltende Therapie im Fall von pCR
 - Sentinel-Node-Biopsie alleine
- Radiotherapie
- Postoperative Systemtherapie wie nicht inflammatorisch

		++
2c	B	++
2c	B	+
2c	B	++
2b	B	++
2b	B	++
2b	B	+
2b	C	+/-
2c	B	++
2b	C	+/-
3b	C	- -
2c	B	++
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 +
- **Morbus Paget mit Mamma-Tumor
(invasives MaCa, DCIS)**
 - **Therapie entsprechend Standards der Grunderkrankung** 5 D ++
 - **Operation mit R0 Resektion** 1c B ++
 - **Weite Exzision (wie bei DCIS) + Bestrahlung** 2b B +
- **Isolierter Morbus Paget des NAC:**
 - **Operation mit R0-Resektion** 1c B ++
 - **R0-Resektion, keine adjuvante Bestrahlung** 4 D ++
 - **Sentinel-Lymphknoten-Exzision (SNE)** 2b B -

Maligner Phylloiddtumor

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**Oxford / AGO
LOE / GR**

- | | | | |
|---|-----------|----------|------------|
| ➤ 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)**

3a	C	--
3a	C	++
3a	C	++
3a	C	--
4	D	++
3a	C	++
3a	C	++
3a	C	+/-
3a	C	-
3a	C	+/-
4	C	+/-

Therapie des Lokalrezidivs:

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

4	C	++
4	C	+/-

Fernmetastasierung/ nicht resektable Tumoren:

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

4	C	++
2b	B	+
4	C	+/-
2b	B	+

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Brustkrebs Nachsorge

START

Brustkrebs Nachsorge

- **Versionen 2002–2014:**
**Bauerfeind / Bischoff / Blohmer /
Böhme / Costa / Diel / Gerber / Hanf /
Heinrich / Janni / Kaufmann / Kümmel /
Lux / Möbus / Mundhenke / Oberhoff /
Scharl / Solomayer / Thomssen**

- **Version 2015:**
Maass / Rody

Brustkrebs Nachsorge

Ziele I

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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 -

* Das lokoregionäre Rezidiv ist mit einem erhöhten Mortalitätsrisiko bei nodalpositiven, PR positiven, jüngeren Patientinnen und einem kurzen Zeitintervall von Erstdiagnose bis Rezidiv verbunden

Brustkrebs-Nachsorge

Ziele II

**Oxford / AGO
LoE / GR**

- | | |
|---|---------------|
| ➤ Verbesserung der Lebensqualität | 2b B + |
| ➤ Verbesserung der körperlichen
Leistungsfähigkeit | 2b B + |
| ➤ Reduktion therapiebedingter Nebenwirkungen
wie z.B. Osteoporose, Herzinsuffizienz,
Fatigue, Neurotoxizität, Lymphödeme | 2b B + |

Brustkrebs-Nachsorge

Ziele III

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

➤ 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, prophylaktische Operationen, Brustrekonstruktion)

2c C +

Brustkrebs Nachsorge Ziele

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

Oxford / AGO

LoE / GR

- | | | | |
|---|-----------|----------|-----------|
| ➤ Einstellung Diabetes mellitus (Typ II)
(> 25% unerkannter DM bei postmenopausalem MaCa) | | | ++ |
| ➤ Gewichtsintervention
(bei BMI <18,5 und >40) | 2a | B | + |
| ➤ Fettreduzierte Diät (mindestens 15 % Kalorienreduktion durch Fett) ist mit einem verbesserten Gesamtüberleben bei HR neg. Patientinnen verbunden | 2b | B | + |
| ➤ Intervention bei Nikotinabusus
(durch Rauchen 2x erhöhte brustkrebsspezifische, 4x erhöhte nicht-brustkrebsspezifische Mortalität) | 2b | B | ++ |
| ➤ Alkoholkonsum reduzieren unter 6 d/d | 2b | B | + |
| ➤ Moderate Sportintervention bei Bewegungsmangel
(Rel. Reduktion der Mortalität um bis zu 25%) | 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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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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➤ 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

**Oxford / AGO
LoE / GR**

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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LoE / GR

Sonstige Zweitkarzinome:

Kolorektal RR 3,0; Endometrium RR 1,6
Ovar RR ca. 1,5; Lymphome RR 7

- 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 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.**

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Loko-regionäres Rezidiv



Loko-regionäres Rezidiv

- **Version 2002:**
Brunnert / Simon
- **Versions 2003–2014:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Lisboa / Maass /
Mundhenke / Rezai / Solomayer / Souchon
/ Thomssen**
- **Version 2015:**
Fersis / Harbeck

Loko-regionäres Rezidiv Inzidenz und Prognose

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Lokalization	Häufigkeit (%)	5-Jahres- Überleben (%)
Ipsilateral Rezidiv¹ (post BOT + Bestrahlung	10 (2–20)	65 (45–79)
Thoraxwand¹ (nach Mastektomie)	4 (2–20)	50 (24–78)
supraclavicular Region²	34%	49% (3-y. OS)
Axilla:		
nach ALND¹	1 (0.1–8)	55 (31–77)
nach SNB⁴	1	93%
Multiple Lokalization²	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

Loko-regionales Rezidiv Staging

Oxford AGO
LoE / GR

Untersuchungen vor Behandlung:

- **Histologische Sicherung** **5 D**
++
- **Reevaluierung von ER, PR, HER2** **3b B**
++
- **Komplettes Re-Staging** **5 D** **++**

Loko-regionäres Rezidiv

Risikofaktoren bei Primärdiagnose

**Oxford
LoE**

Erhöhtes Risiko für ein lokoregionäres Rezidiv

- | | |
|---|------------|
| ➤ Junges Alter | 1a |
| ➤ Positive mikroskopische Ränder | 1a |
| ➤ Unterlassene Strahlentherapie (falls adjuvant indiziert) | 1a |
| ➤ Ausgedehnte intraduktale Komponente | 1b |
| ➤ Gefäßinvasion | 1b |
| ➤ Triple-negativ und HER2+/HR neg. vs. HR pos. | 2a |
| ➤ Grading (G3 vs. G1) | 1b* |
| ➤ Erhöhte Proliferationsmarker (z.B. Ki67) | 2b |
| ➤ pT (> 2 vs. ≤ 2 cm) | 1b* |
| * nodal negativ | 1a |
| ➤ pN (N1 vs. N0) | 1a |
| ➤ Anzahl befallener LK | 1a |
| ➤ Inflammatorisches Mamma-Ca | 2b |
| ➤ Medialer Tumorsitz (vs. zentral/lateral) | 4 |
| ➤ Übergewicht (Body mass index) | 1a |

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**FORSCHEN
LEHREN
HEILEN**

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

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

IBCSG-Studie, 13 randomisierte Studien n = 8106 Patienten

Risikofaktoren für 10 J. kumulative Inzidenz:

...>15% Thoraxwand LK Alter < 40; ≥ 4 pos. Lymphknoten, 0-7 befallene LK

...>10% supraclaviculär: ≥ 4 pos. LK

...>5% axillares Rezidiv: Alter < 40; unknown tumor size, 0-7 nicht befallene

Lymphknoten

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.

Loko-regionäres Rezidiv

Prognostische / Prädiktive Faktoren

Oxford AGO
LoE / GR

Risikofaktoren beim Lokalrezidiv für das Auftreten eines Re-Rezidivs

➤ Tumorgroße

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

Oxford AGO
LoE/GR

➤ 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*

1b B +/-

➤ Palliative Operation in der M1-Situation

5 D +

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

* Falls kein Sentinel identifiziert wird, sollte keine Axilladisektion erfolgen; keine Operation außerhalb der ipsilateralen Axilla wird empfohlen.

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Operative Therapie

Oxford AGO
LoE / GR

- | | |
|---|--------------------|
| ➤ 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 + |

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Lokoregionäres Rezidiv nach R0-Resektion – Systemische Therapie

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

Oxford AGO
LoE / GR

- 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

n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection

5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy vs. 57% (44-67) without chemotherapy (hazard ratio 0.59 [95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).

Adjuvant chemotherapy was significantly more effective in ER negative disease (p_{interaction}=0.046).

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

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

**Oxford AGO
LoE / GR**

➤ **Endokrine Therapie bei endokrin
responsiblen Tumoren**

2b B ++

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

2b B ++

➤ **Bei HER2-überexprimierenden
Tumoren**

HER2-zielgerichtete Therapie mit Chemotherapie

5 D ++

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)
- **Dosisescalation der Bestrahlung**

2b B +/-

3b C -

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Lokale Behandlung

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LoE / GR

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

Oxford AGO
LoE / GR

➤ 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	+/-

* In Zentren, die auf der DKG-Website gelistet sind

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Endokrine und zielgerichtete Therapie des metastasierten Mammakarzinoms

START

Endokrine Therapie des metastasierten Mammakarzinoms

- **Version 2002:**
Gerber / Friedrichs
- **Versionen 2003–2014:**
**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat /
Kaufmann / Loibl / Lück / von Minckwitz /
Müller / Mundhenke / Nitz / Schneeweiß /
Schütz / Stickeler**
- **Version 2015:**
Liedtke / Möbus

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/PR und HER2 Metastase vs. Primärtumor

Metaanalyse basierend auf 48 (überwiegend retrospektiven) Analysen:

Gepoolte relative Diskordanz

- 20% (95%CI 16-35%) for ER
- 33% (95%CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Wechsel der Rezeptorexpression von positiv zu negativ und von negativ zu positiv

- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2

Endokrine Therapie der prämenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom

**Oxford / AGO
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	+
➤ GnRH-A. + Fulvestrant	4	C	+/-
➤ Aromataseinhibitoren ohne OFS	3	D	- -

Endokrine Therapie

der postmenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom

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	+/-
➤ Letrozol + Palbociclib (vs. Letrozol)	2b	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 in der Erstlinientherapie eingesetzt werden.

Endokrine Therapie der postmenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom (nach adjuvant Tamoxifen oder ohne adjuvante endokrine Therapie)

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Behandlungssequenz

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

Oxford / AGO LoE / GR

1a	A	++
2b	C	+/-
1b	B	
1b	B	++
2b	B	+/-
1b	A	++
2b	B	+
2b	B	+
3b	C	+
4	D	+/-
3b	C	+/-
5	D	+/-

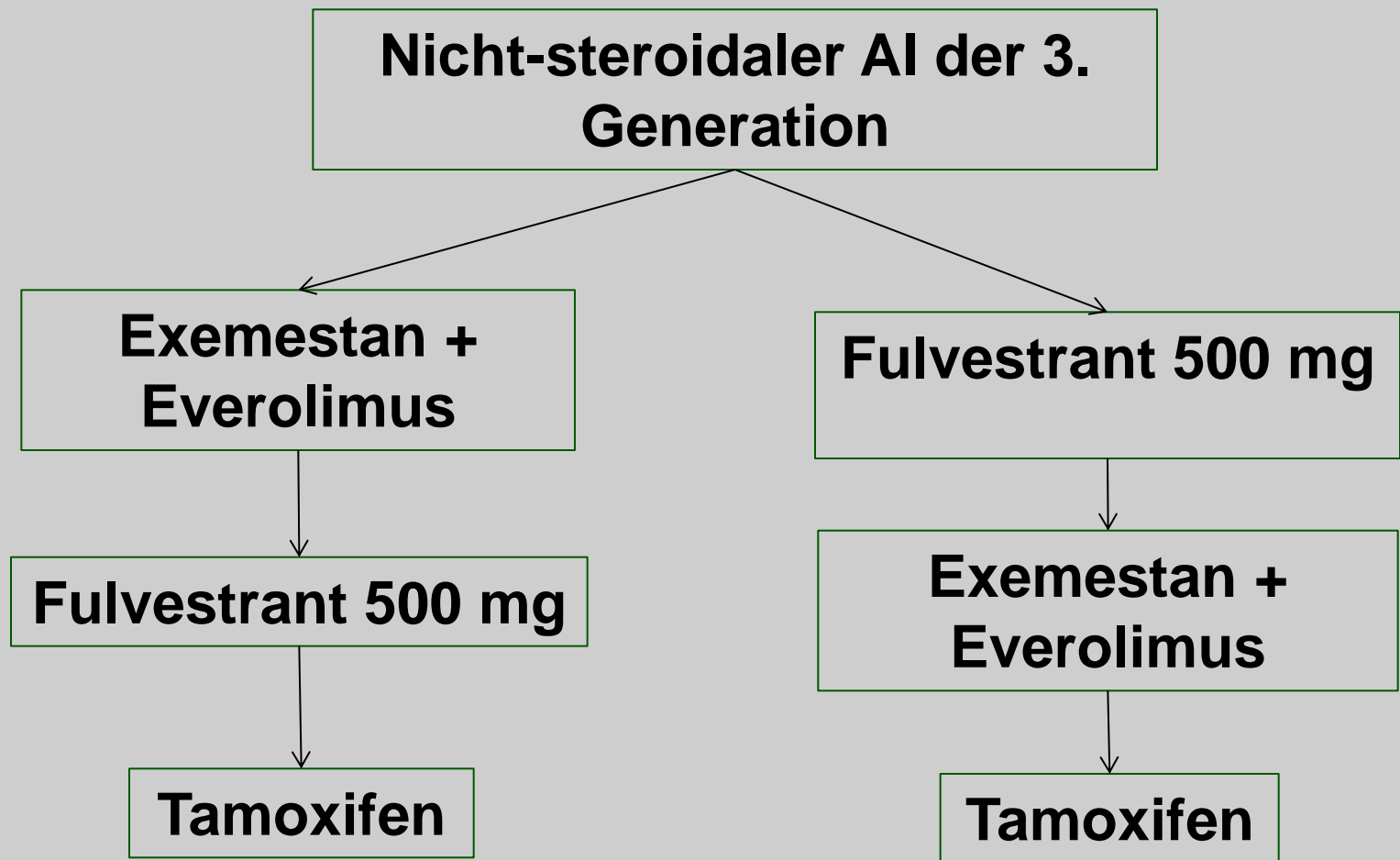
*Es gibt keine Hinweise für die Überlegenheit eines einzelnen Aromataseinhibitors

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

Therapiealgorithmen nach adjuvanter Tamoxifentherapie

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Endokrine Therapie

der postmenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom (nach adjuvanter Therapie mit einem AI)

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
- Wiederholung einer Vortherapie

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

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

Endokrine Therapie der postmenopausalen Patientin mit HER2 negativem metastasiertem Mammakarzinom in Kombination mit Bevacizumab

Oxford / AGO
LoE / GR

- **Erhaltungstherapie mit Bevacizumab plus endokrine Therapie nach Remission unter Chemotherapie mit Bevacizumab**
- **Bevacizumab plus endokrine Therapie als Erstlinientherapie bei lokal fortgeschrittener oder metastasierter Erkrankung**

2b^a B +

1b^a B -

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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

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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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 und Lapatinib	1b^a	B	-

**Geringe Wirksamkeit einer alleinigen endokrinen Therapie.
Eine Chemotherapie mit einer anti-HER2-Therapie sollte
in Erwägung gezogen werden!**

Kombination von endokriner Therapie mit anti-HER2-Therapie

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Behandlung (Anzahl Pat)	PFS (Monate)	Ansprechen (CBR)	OS (Monate)
Trastuzumab + anastrozol vs. anastrozol (n=207)	4.8 vs. 2.4 (5.6 vs. 3.8 bei zentral bestätigten Receptorstatus)	42.7% vs. 27.9%	28.5 vs. 23.9 Monate; n.s.
Trastuzumab + letrozol vs. letrozol (n=57)	14 vs. 3.3	27% vs. 13%	n.r.
Lapatinib + letrozol vs. letrozol (n=219/1286)	8.2 vs. 3.0	48% v 29%	33.3 vs. 32.3 Monate
Lapatinib + fulvestrant vs fulvestrant (n=267/324)	4.1 vs. 3.8 (HER2-) 5.9 vs. 3.3(HER2+)	38 vs. 17%	30 vs. 26.4 (alle)

Simultane oder sequenzielle endokrin-zytostatische Behandlung

Oxford / AGO
LoE / GR

➤ **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

* Es werden nur Substanzen mit publizierten Studienergebnissen basierend auf zumindest einer publizierten Studie Phase III oder IIb berücksichtigt.

Chemotherapie mit oder ohne zielgerichtete Substanzen bei metastasiertem Mammakarzinom

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- **Version 2002:**
von Minckwitz / Schaller / Untch
- **Version 2003–2014:**
**Bischoff / Dall / Fersis / Friedrichs /
Harbeck / Jakisch / Janni / Möbus / Rody /
Scharl / Schmutzler / Schneeweiss /
Schütz / Stickeler / Thomssen**
- **Version 2015:**
von Minckwitz / Müller

Chemotherapie

Krankheitsfreies und Gesamtüberleben

**Oxford / AGO
LOE / GR**

- **Eine Verbesserung der Überlebenszeit beim metastasierten Mammakarzinom wurde in einigen retrospektiven Analysen gezeigt** **2a**
- **Allerdings haben Patientinnen mit einer metastasierten Erkrankung heute mehr adjuvante Therapie erhalten und müssen deshalb als therapieresistenter angesehen werden** **2a**
- **Mehrere Linien der sequenziellen Therapie sind von Vorteil (gleiche Wirksamkeit, geringere Toxizität)** **1b**
- **Besonders für Kombinationen einer Chemotherapie mit zielgerichteten Substanzen wurde ein entsprechender Überlebensvorteil festgestellt** **1b**

Therapie des metastasierten Mamma- karzinoms – Prädiktive Faktoren

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Therapie	Faktor	Oxford / AGO LOE / GR		
Endokrine Therapie	ER/PR Rezeptorstatus (Primärtumor, Metastase) vorheriges Ansprechen	1a	A	++
		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 potenzielle 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

Oxford / AGO
LOE GR

**Solange wie der therapeutische Index
positiv bleibt**

- Therapie bis zur Progression
- Therapie bis zum besten Ansprechen
- Wechsel auf alternatives Schema
vor einer Progression

1a A ++

2b B +

2b B +/-

2b B +/-

➤ Therapiestopp bei

- Progression
- Nicht tolerabler Toxizität

1c A ++

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)**
- **Rezidivfreies Intervall nach Ende der adjuvanten Therapie**
- **Aggressivität der Erkrankung, Lokalisation der Metastasen**
- **Geschätzte Lebenserwartung**
- **Begleiterkrankungen (einschließlich Organfunktionen)**
- **Erwartungen und Präferenzen der Patienten**

mBC – HER2-negativ/HR-positiv

Palliative Chemotherapie

Erstlinienbehandlung*

Oxford / AGO
LOE / GR

Mono-Therapie:

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

1b	A	++
1b	A	++
3b	B	+
2b	B	+
2b	B	+

Poly-Chemotherapie:

- A + T
- Paclitaxel + Capecitabin
- Docetaxel + Capecitabin nach adj. A
- T + Gemcitabin nach adj. A
- A + C oder A_{lip} + C

1b	A	++
2b ^a	B	+
1b	A	+
2b	B	++
1b	B	++

Berücksichtigung der Vorbehandlung:

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

mBC HER2-negativ / HR-positiv

Palliative Chemotherapie

nach Anthrazyklin-Vorbehandlung*

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

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

mBC HER2-negativ / HR-positiv

Palliative Chemotherapie

nach Taxan- und Anthrazyklin-Vorbehandlung

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➤ Experimentelle Therapien in Studien

➤ Capecitabin

➤ Eribulin

➤ Vinorelbin

➤ (Peg)-liposomales Doxorubicin

➤ Gemcitabin + Cisplatin / Carboplatin

➤ Gemcitabin + Capecitabin

➤ Gemcitabin + Vinorelbin*

Oxford / AGO
LoE / GR

++

2b B ++

1b B ++

2b B ++

2b B +

2b B +/-

2b B +/-

1b B -

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***Cave Neutropenie / Therapeutischer Index!**

Triple-negatives metastasiertes Mammakarzinom

**Oxford / AGO
LoE / GR**

- **Experimentelle Therapien innerhalb von Studien** ++
- **Chemotherapie wie bei Patientinnen mit HR-pos / HER2-neg mBC** +
- **Carboplatin (vs. Docetaxel)** 1b^a B +/-
 - **bei gBRCA Mutation** 1b^a B +
- **Gemcitabin/Cisplatin (vs. GemPac)** 1b^a A +
- **Bevacizumab zusätzlich zur first-line Zytostatikatherapie** 2b B +

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Bevacizumab beim HER2-neg. metastasierten Mammakarzinom

Oxford / AGO LoE / GR

➤ 1st line in Kombination mit:

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

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

➤ Cap+Bev as maintenance after Doc+Bev

1b	B	+/-
----	---	-----

➤ 2nd line as treatment through multiple lines

1b	B	+/-
----	---	-----

➤ 2nd line in Kombination mit:

- Taxanen
- Capecitabine
- Gemcitabine oder Vinorelbine

1b	B	+/-
1b	B	+/-
1b	B	-

Erstlinientherapie beim HER2 pos. metastasierten Mammakarzinom

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	Oxford / AGO LoE / GR		
➤ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
➤ Paclitaxel + Trastuzumab + Pertuzumab	2b	B	+
➤ T-DM 1 (Rückfall innerhalb von 6 Monaten und nach Taxan und Trastuzumab	2b	B	+
➤ 1 st line Chemotherapie* + Trastuzumab	1b	B	+
➤ Trastuzumab mono	2b	B	+/-
➤ Taxan + Lapatinib	1b ^a	B	-
➤ Taxanes + trastuzumab + everolimus	1b ^a	B	-
➤ Trastuzumab + Aromatase-Inhibitoren (ER+)	2b	B	+/-**
➤ Lapatinib + Aromatase-Inhibitoren (ER+)	2b	B	+/-**

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

**siehe Kapitel Endokrin +/- targeted

2nd line Therapie bei HER2 pos. mBC (nach Vorbehandlung mit Trastuzumab)

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	Oxford / AGO LoE / GR		
➤ T-DM 1	1b	A	++
➤ TBP: 2nd line Chemotherapie + Trastuzumab	2b	D	+
➤ Capecitabine + Lapatinib	1b	B	+
➤ Trastuzumab + Lapatinib (HR neg. tumor)	2b	B	+
➤ Taxane + Trastuzumab + Pertuzumab	5	D	+
➤ Jede andere 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**

**Oxford / AGO
LoE / GR**

1b A ++

1b B +

2b B +

2b B +

2b B +

1b B +/-

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

- **Experimentelle Anti-HER2-Regime** **5 D +**
- **Für Patienten nach Trastuzumab und Pertuzumab Vorbehandlung, Therapie gemäß obenstehender Empfehlungen** **5 D**

Lapatinib beim HER2-positiven metastasierten Mammakarzinom

**Oxford / AGO
LoE / GR**

In Kombination mit

➤ **Trastuzumab für schwer vorbehandelte Patientinnen**

2b B +

➤ **Paclitaxel als 1st line**

2b B -

➤ **Capecitabine als > 2nd line**

1b B +

➤ **AI bei ER positiver Erkrankung**

2b B +/-

➤ **Bei Patientinnen mit Hirnmetastasen (Radioresistenz) in Kombination mit Capecitabine**

2b B +/-

Immundiagnostik und Immuntherapien

Immundiagnostik:

- **Bestimmung von:**
 - Immunologischen Parametern im peripheren Blut

Oxford / AGO
LoE / GR

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
- Immunomodulation (z.B. Zugabe von Nov-2 zur Chemo AC –T)
- Intradermale Vakzinierung von Dendritischen Zellen
- Aktive Vakzinierungen
- Passive Vakzinierungen
- Therapie mit Onkoviren
- Zytokine
- Checkpoint inhibitors (PD1; PDL-1;...)

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Osteoonkologie und Knochengesundheit

Osteoonkologie und Knochengesundheit

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Huober / Jackisch / Janni / Lux / Maas /
Nitz / Oberhoff / Schaller / Scharl / Schütz
/ Seegenschmiedt / Solomayer / Souchon**
- **Version 2015:**
Fehm / Hanf

Bisphosphonate beim Mammakarzinom

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 | 2b | C | +/- |
| (bei Frauen unter BP-Therapie mit niedriger Knochendichte) | | | |

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Denosumab beim Mammakarzinom

Oxford / AGO LoE / GR

- | | | | |
|---|-----------|----------|------------|
| ➤ Reduktion der Hyperkalzämie | 1a | A | ++ |
| ➤ Reduktion skelettaler Komplikationen | 1a | A | ++ |
| ➤ Reduktion von Knochenschmerzen | 1a | A | ++ |
| ➤ 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	++
➤ Zoledronat i.v. 4 mg q12w*	1b ^a	B	+
➤ Denosumab 120 mg s.c. q4w	1a	A	++
➤ Andere Dosierungen oder Schemata, wie z.B. aus den Studien zur adjuvanten Situation oder Osteoporosetherapie	5	D	--

* für Patientinnen, die bereits 1 Jahr oder länger Zoledronat 4mg q4w erhalten haben

Ossäre Metastasen

Radionuklidtherapie

Oxford / AGO
LoE / GR

- **Tumorprogression nach Ausschöpfung der Standardtherapie multipler / disseminierter Skelettmetastasen und intolerabler Knochenschmerzen**

	1b	B	+
--	-----------	----------	----------
- **¹⁸⁶Rhenium-hydroxyethyliden-diphosphonat**

	2b	B	+
--	-----------	----------	----------
- **¹⁵³Samarium**

	1b	B	+
--	-----------	----------	----------
- **⁸⁹Strontium**

	1b	B	+
--	-----------	----------	----------
- **²²³Radium**

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

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) sowie 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**
- **Verbundosteosynthesen (Osteosynthese und Einbringen von PMMA)**
- **Wirbelkörperersatz durch Titanspacer**
- **Tumorendoprothesen**
- **Vertebroplastie / Kyphoplastie +/- Thermoablation des Tumors**
- **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

Rekurrenter Knochenschmerz in vorbestrahlten Arealen des Skeletts

**Oxford / AGO
LoE / GR**

➤ Einmalige RT *	3b	C	++
➤ Fraktionierte RT *	3b	C	+
➤ Radionuklidtherapie	3b	C	+
➤ MR-gesteuerter hochfokussierter Ultraschall	1b	B	+

* Dosis und Fraktionierung hängt von der Lokalisation, vom Intervall zur letzten Strahlentherapie sowie von Dosis und Fraktionierung der ersten Strahlentherapie ab.

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

Oxford LoE

- **Nierenfunktionsstörungen durch i.v. Amino-Bisphosphonate** 1b
- **Kieferosteonekrose (ONJ) typisch unter i.v. BPs und Denosumab (1,3%/1,8%)** 1b
 - **Assoziation mit (parallelem) Einsatz von anti-angiogenetischen Therapien** 3b
- **Ausgeprägte Fälle mit Hypokalzämie (Dmab>BP)** 1b
- **Akut-Phase-Reaktion (i.v. Amino-BPs und Denosumab) 10-30%** 1b
- **Gastrointestinale Nebenwirkungen (orale BPs) 2-10%** 1b
- **Atypische Femurfrakturen (absolutes Risiko: 11 pro 10.0000 Personenjahre mit BP-Einnahme)** 2b

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
- Gute Zahnhygiene, nur mässiger Alkoholkonsum sowie Nikotinverzicht

Unter adjuvanter Bisphosphonattherapie ist das Risiko für Kieferosteonekrosen gering

Adjuvante Bisphosphonattherapie zur Verbesserung des Überlebens

Oxford / AGO
LoE / GR

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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**FORSCHEN
LEHREN
HEILEN**

Dosierung adjuvanter Bisphosphonate zur Verbesserung des Überlebens

- **Nicht-Aminobisphosphonate:**
- **Clodronat p.o. 1600 mg/d (Bonefos/ Clodronsäure)**
- **Clodronat p.o. 1040 mg/d (Ostac)**
- **Aminobisphosphonate:**
- **Zoledronat i.v. 4 mg/6 m (Zometa/ Zoledronsäure)**
- **Ibandronat p.o. 50 mg/d (Bondronat/ Ibandronsäure)**
- **Pamidronat p.o. (in oraler Form in D nicht verfügbar)**
- **Risedronat p.o. 35 mg/w (Actonel/ Risedronsäure)**
- **Alendronat p.o. 70 mg/w (Fosamax/ Alendronsäure)**
- **Optimale Dauer der adjuvanten BP-Gabe muss noch definiert werden (in den Studien Dauer der BP: 2-5 Jahre)**

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

5 D -

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

2b B +

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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. D3 (800–2000 U/d)	4	C	++
➤ Nikotinverzicht, nur mäßiger Alkoholkonsum	2b	B	++
➤ Vermeidung eines BMI < 20 kg/m ²	3b	C	++
➤ Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage)			

Medikamentöse Therapie der Osteoporose

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	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 (nur Wirbelsäule)	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	++

* wurden bei MammaCa-Patientinnen mit Tumorthherapie assoziierter Osteoporose getestet

** erhöhtes Risiko für Myokardinfarkte.; nur bei postmenopausalen Patientinnen mit schwerer Osteoporose und hohem Frakturrisiko

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROTHERAPIE NACH RISIKOPROFIL in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.¹

Lebensalter in Jahren		T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score > -2,0 nicht sicher belegt.)				
Frau	Mann ²	-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

¹ Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).

² bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

Therapieindikation auch schon bei um 1,0 höherem T-Score ^{3,4}, wenn:

- Glukokortikoide oral $\geq 2,5$ mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Besondere Situationen und Lokalisationen in der metastasierten Situation

Besondere Situationen und Lokalisationen in der metastasierten Situation

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- **Version 2002:**
Dall / Fersis / Friedrich
- **Versionen 2003–2014:**
Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Fehm / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon
- **Version 2015:**
Bischoff / Diel

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 aufgetretener Oligometastasierung | 3 | D | + |
| ➤ Lokale Behandlung bei Schmerzen, Exulzation, Ileus, persistierende Metastase(n) nach Abschluss der Systemtherapie, Hydrocephalus occlusus, spinale Kompressionssyndrom | 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

2 B +/-

5 C +/-

5 C -

* insbesondere bei Knochenmetastasen

Hepatische Metastasen

Lokale Therapie

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|------------|
| ➤ Chirurgische Resektion (R0) | 3b | C | +/- |
| Individuelle Fälle (Leberfunktion) mit resektablen Metastasen | | | |
| HR positiv; Chemotherapie sensibel | 4 | C | +/- |
| ➤ Regionale Chemotherapie | 3b | C | +/- |
| ➤ Regionale Radiotherapie | 4 | C | +/- |
| (SIRT, Radiochemoembolisation, andere Bestrahlungsverfahren) | | | |
| ➤ Thermoablation | 3b | C | +/- |
| (RFA, LITT, Kryotherapie) | | | |

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

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)

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LoE / GR**

Wöchentliche Chemotherapie*:

Epirubicin, Doxorubicin, Paclitaxel

4 D ++

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 + |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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ZNS-Metastasen beim Mammakarzinom



ZNS-Metastasen beim Mammakarzinom

- **Versionen 2003–2014:**
**Bischoff / Diel / Friedrich / Gerber /
Lück / Maass / Müller / Nitz / Jackisch /
Jonat / Junkermann / Rody / Schütz**

- **Version 2015:**
Jackisch / Huober

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**

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 >= 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 vs. 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 $> \sim 3$ cm 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 (> 3 Läsionen)

Oxford / AGO LoE / GR

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

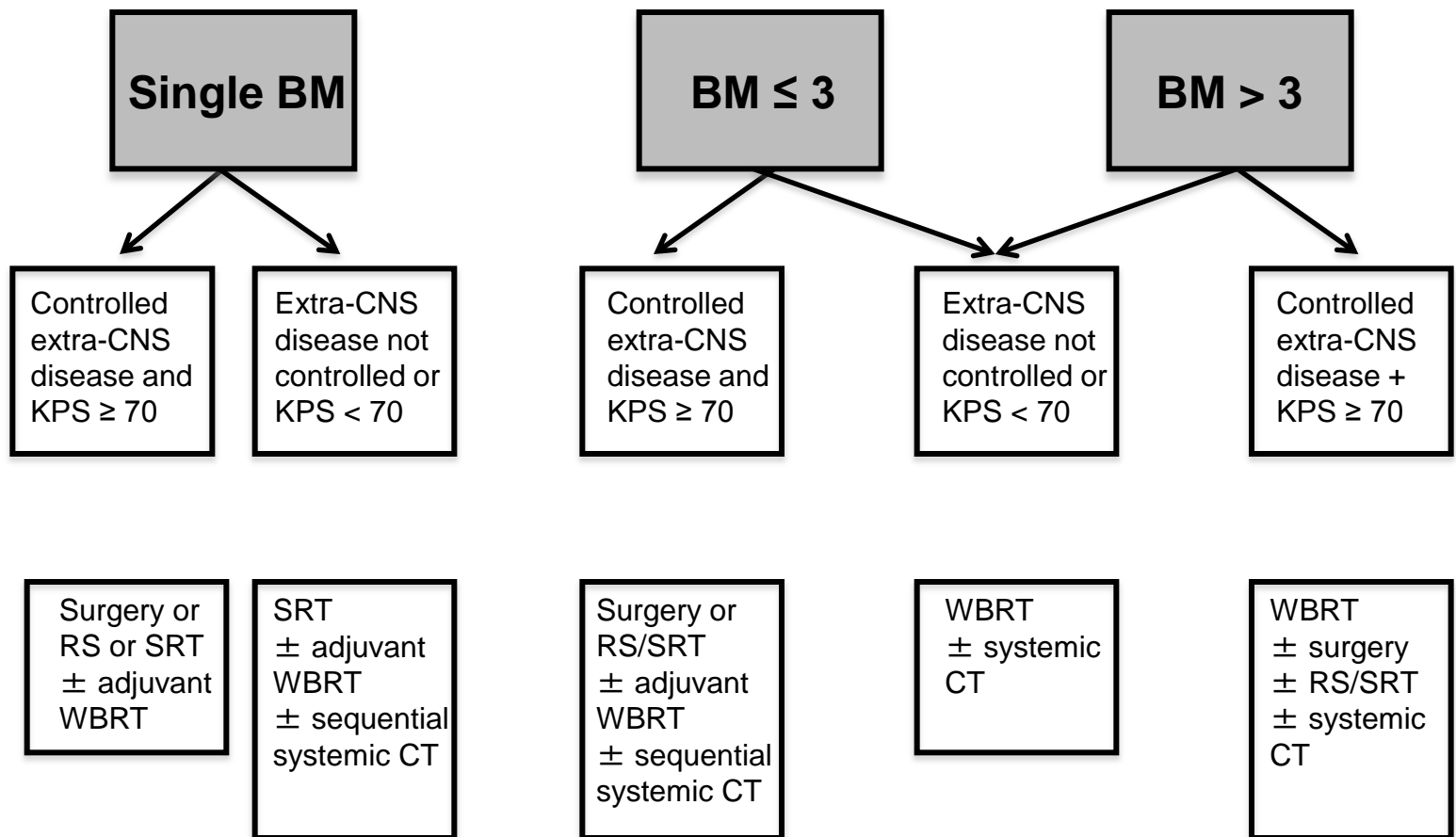
1a	A	++
3b	B	++
3b	C	+/-
3a	D	+/-
3a	B	+/-

Bei Radioresistenz / Rezidiv:

- **Chemotherapie allein**
- **Lapatinib +/- Capecitabin (HER2 pos. Fälle)**
- **T-DM1 (HER2 pos. Fälle)**
- **Erneute Strahlentherapie (falls möglich)**
*symptomadaptiert

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

Mögliche Behandlungsstrategie für Hirnmetastasen eines Mammakarzinoms*



BM: brain met.
CT: chemotherapy

RS: radiosurgery
SRT: stereotactic radiotherapy

WBRT: whole brain radiotherapy

Systemische und symptomatische Therapie von Hirnmetastasen

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LoE / GR

- | | | | |
|--|----|---|-----|
| ➤ Fortsetzung der anti-HER2-Therapie im Falle einer extrakranialen Remission | 2c | C | + |
| ➤ Lapatinib + Capecitabin als initiale Behandlung (HER2 pos. Fälle) | 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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Leptomeningeosis carcinomatosa

Lokale Therapie

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Intrathekale oder intraventrikuläre Therapie

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

- Liposomales Cytarabin 50 mg, q 2w
- Thiothepa
- Steroide
- Trastuzumab (HER2 pos. Fälle)

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2b B ++

3b C ++

3b C +

4 D +/-

4 C +/-

Radiotherapie

- Fokal (bei größerem Tumolvolumen)
- WBRT
- Neuroaxe (disseminierte spinale Herde)

4 D +

4 D +

4 D +/-

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

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Komplementäre Therapie

„Survivorship“

START

Komplementäre Therapien

Hormontherapie

„Survivorship“ (Rezidiv-Prävention)

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- **Versionen 2002–2014:**
**Albert / Bauerfeind / Blohmer / Fersis /
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Kümmel / von Minckwitz / Oberhoff / Scharl
/ Schmidt / Schütz / Thomssen**

- **Version 2015:**
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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*

Allgemein

Oxford AGO

LoE / GR

- | | | | |
|--|-----------|----------|-----------|
| ➤ Komplementär-alternative Methoden (CAM)
anstelle chirurgischer Interventionen | 5 | D | -- |
| ➤ Komplementär-alternative Methoden (CAM)
anstelle systemischer Therapie | 2b | B | -- |
| ➤ <u>Unter Systemtherapie: Besondere Beachtung gilt möglichen
Medikamenteninteraktionen</u> | | | |

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Komplementäre Therapien prä- und postoperativ

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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 I

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

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- **Mistellektine** (*Viscum album*)
(zur Reduktion von therapieassoziierten Nebenwirkungen)
(Einfluss auf Antitumorthherapie unbekannt)
- **Thymuspeptide**
(verringern Risiko schwerer Infektionen)
(Einfluss auf Antitumorthherapie unbekannt)
- **Ginseng (Krebs-assoziierte Fatigue)**
(Ginseng inhibiert u.a. CytochromP Enzyme
z.B. CYP3A4)
- **Ganoderma Lucidum**
- **L-Carnitin (Prävention der Toxizität, Verbesserung
periphere Neuropathie)**
- **L-Carnitin (keine Verbesserung der Fatigue)**
- **Ingwer** (Chemotherapie induzierte Übelkeit/Erbrechen;
cave: Wechselwirkungen)

1a B +/-

2a B +/-

2b C -

2b C -

1b B --

1b B --

1b C +/-

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

zur Behandlung chemotherapiebedingter Nebenwirkungen

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

1b B -

➤ Homöopathische Medizin

gegen therapiebedingte Nebenwirkungen

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

1b B +/-

➤ 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

1a 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, kein höheres
Risiko für die Entstehung von Lymphödemen

1a A ++

Komplementäre Therapien

Behandlungsphase - Mind-Body Medizin II

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Yoga

Verbesserung von Lebensqualität, Stress, Angst und Depression

1b A +

Verbesserung von Fatigue

1b A +/-

Qigong

Hinweise auf Verbesserung von Lebensqualität, Fatigue, Stimmung

2a B +/-

Tai-Chi

Verbesserung von Lebensqualität, Muskelstärke,

2a B +/-

Hypnose (in Kombination mit kognitiver Therapie)

Verbesserung von Fatigue und Muskelanspannung unter Radiotherapie, Reduktion von Distress

1b A +

Komplementäre Therapien

Rezidiv-Prävention I

Beeinflussbare Lebensstilfaktoren – Sport - Genussmittel

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LoE / GR

➤ **Körperliches Training / Sport**

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

1a A ++

➤ **Nikotinabusus**

1b A -

➤ **Alkohol (>6 g/die)**

1b A -

Komplementäre Therapien

Rezidiv Prävention II

Beeinflussbare Lebensstilfaktoren - Ernährung

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- **Anstreben eines normalen BMI/
Abnehmen bei Übergewicht, unabhängig
vom HR Status**
(verbessert Prognose – DFS/OS)
- **Ernährung mit geringem Fettanteil**
(verbessert Prognose – DFS-OS,
Ernährungsberatung empfohlen)
- **Vermeidung stark fetthaltiger Diätprodukte**
- **Lignan-/Ballaststoff-haltige Lebensmittel**
(u.a. Saaten z.B. Leinsamen)
- **Beachten genereller Ernährungs-
empfehlungen** (z.B. von DGE, WCRF)
- **Diät-Extreme**
(are associated with less favourable
outcomes)

1a A ++

1a A +

2b C +

2a B +

2a B ++

1b B - -

Komplementäre Therapien

Rezidiv-Prävention III

Pflanzliche Therapieansätze - Nahrungsergänzung

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➤ Nach Systemtherapie – Vitamine/Antioxidantien scheinen nicht mit einem erhöhtem Rezidivrisiko assoziiert	2b	B	
➤ Raucher haben ein höheres Bronchial-Ca-Risiko unter Antioxidantien	1b	A	
<u>Prävention eines brustkrebsassoz. Rezidivs</u>			
➤ Antioxidanzien	2a	B	+/-
➤ Orthomolekulare Substanzen (Selen, Zink...)	5	D	-
➤ Vitamine (zusätzlich zu ausgewogener Ernährung; Vit C, E, D)	2a	B	+/-
➤ Karotenoide erscheinen mit schlechterem Ergebnis assoziiert	2b	B	-
➤ Proteolytische Enzyme (Papain, Trypsin, Chymotrypsin)	3b	B	-
➤ Sojaprodukte (Phytoöstrogene)	2a	B	+/-
➤ Konzentration ≥ 100 mg Isoflavone	2a	B	-
➤ Traubensilberkerze (Cimicifuga racemosa)	2a	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

Verminderung von Karzinomschmerzen

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

CAVE: Keine Verzögerung der Diagnostik!

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Gynäkologische Probleme bei Mammakarzinompatientinnen

START

FORSCHEN
LEHREN
HEILEN

Gynäkologische Probleme bei Mammakarzinompatientinnen

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➤ Version 2015:

Loibl / Gerber

**(unter Mitarbeit von Hanf / Kümmel und Stickeler /
Scharl)**

Hormon-(Ersatz-)Therapie (HT) für Östrogenmangelsymptome nach Mammakarzinom-Diagnose und -Therapie

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➤ Hormonsensitive Erkrankung (rezeptorpos.) (Prognoseverschlechterung durch HT mögl.)	1b B	-
➤ Nicht-hormonsensitive Erkrankung (rez.neg.) (wahrsch. keine Prognoseverschlechterung)	2a B	+/-
➤ Hormonsensitive Erkrankung (rez.pos.): komb. Therapie TAM plus niedrig dos. HT	2b B	+/-*
➤ Tibolon	1b A	--
➤ Topisch vaginale Applikation von		
➤ Östriol (E3)	4 D	+/-
➤ Östradiol (E2) während einer AI-Therapie	4 C	-

***Studienteilnahme empfohlen**

Weitere Methoden zur Erleichterung postmenopausaler Symptome nach Mamma-Ca I

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Medikamentöse Ansätze:

- | | | | |
|--|----|---|-----|
| ➤ Selektive Serotonin-Reuptake-Inhibitoren und Serotonin-(Noradrenalin) Reuptake -Inhibitoren (SSRI-SNRI): zur Reduktion von Hitzewallungen | | | |
| ➤ 1 ^{ste} Wahl: Venlafaxin | 1a | A | + |
| ➤ 2 ^{te} Wahl: Desvenlafaxin | 1b | A | +/- |
| ➤ 3 ^{te} Wahl: Sertralin, Escitalopram | 1b | A | +/- |
| ➤ Gabapentin (MaCa-Pat. unter Tamoxifen-Therapie) | 1b | A | + |
| ➤ Pregabalin | 1b | A | +/- |
| ➤ Clonidin (MaCa-Pat. unter Tamoxifen-Therapie) | 1a | A | + |
| ➤ MPA (i.m. 500 mg als Einzeldosis)
(sehr wirksam, aber endokrin wirkende Substanz!) | 1b | A | +/- |
| ➤ Vitamin E | 1b | A | - |

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	1b	A	-
➤ Traubensilberkerze und Johanniskraut als fixe Kombi	1b	B	+/-
➤ Johanniskraut-Produkte (in Kombinationstherapie) (pharmakologische Interferenz mit endokriner Therapie, Zytostatika und Tyrosinkinase-Inhibitoren)	1b	B	--
➤ Kava-Kava (Piper methysticum)	5	D	--
➤ Rotklee-Blätter (Trifolium pratense)	1b	B	+/-
➤ Dong Quai Wurzel (Angelica sinensis)	5	D	--
➤ Ginseng Wurzel (Panax ginseng or P. quinquefolius)	1b	B	-
➤ Bromelain + Papain + Selen + Lektin (bei AI-induzierten Gelenksbeschwerden)	3b	B	+/-

Komplementäre Therapien

Postmenopausale Symptome I

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Allgemeine Ansätze:

➤ **Körperliches Training / Sport**

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1b B +

➤ **Mind Body-Medizin**

(Yoga, Hypnose, Schulung, Beratung)

1b B +

➤ **Kognitive Verhaltenstherapie**

1b B +

➤ **Akupunktur**

Aromatase-inhibitor treatment induced arthralgia

2b B +

Hot flashes

1b B +

Depression

2b B +/-

Anxiety, Sleep

3b C +/-

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(take note: no acupuncture in tumor bearing region, possibility of cell seeding)

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

Oxford / AGO
LoE / GR

➤ Erhaltung der Ovarialfunktion

➤ CHT + GnRHa

1b B +/-

(GnRHa Applikation > 2 Wochen vor Chemotherapie)

Beeinflussung des Chemoeffektes nicht sicher ausgeschlossen!

➤ Beratung über Fertilitätserhaltung

4 C +

➤ Fertilitätserhalt mit assist. reprod. Therapie

4 C +

Ovarian Function Preservation – Comparison of Randomized Trials

	ZORO	PROMISE	Munster et al. - US	POEMS
Patient number	60 (60 HR-)	281 (50 HR-)	49 (13 HR-) of 124	218 (218 HR-)
Age median	38 years	39 years	39 years	Premenop. < 50 years
Treatment	goserelin	triptorelin	triptorelin	goserelin
Start of treatment	>2 weeks prior to cht	>1 week 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	Ovarian failure at 2 yrs 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%	
Multivar. analysis	age as only independent predictive factor	treatment as only independent predictive factor	n.d.	Treatment as only Independent predicitive factor
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	78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%
Median time to restoration of menses (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	n.d.
Cyclophosph. dose	4600 vs. 4700mg	4080 vs. 4008 mg	n.r.	n.a.

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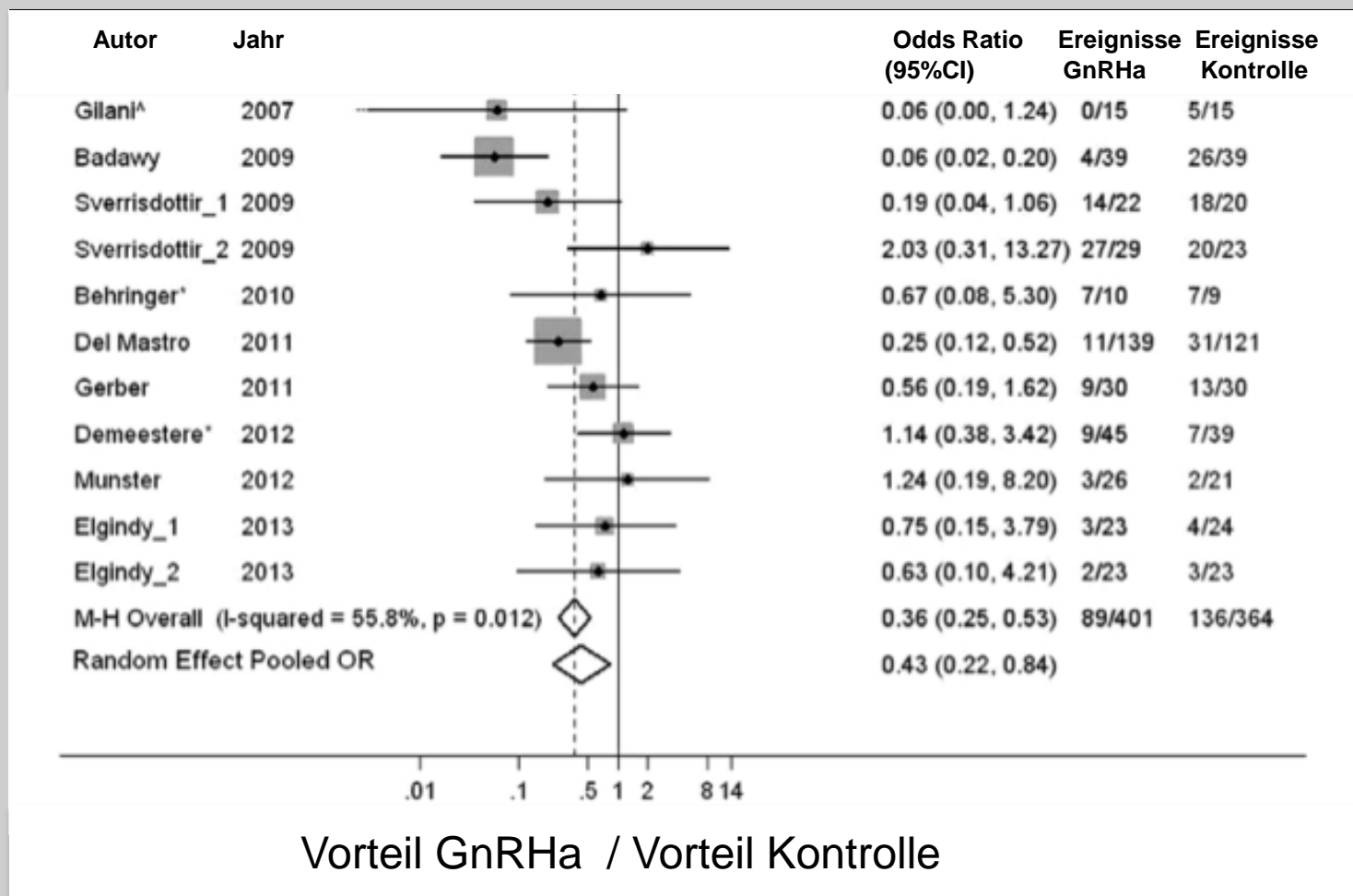
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Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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Testung der ovariellen Reserve

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**Einschätzung der ovariellen Reserve bei
infertilen Patientinnen
(>6-12 Monate ohne Konzeption)***

5 C +

Tests zur Fertilitäts-Beurteilung

➤ **Anti-Müller Hormon**

3b B +/-

➤ **Antrale Follikelzählung**

3b B +/-

* Tests werden vorgeschlagen für Frauen > 35 J und Infertilität für 6-12 Monate; die Tests präzisieren nicht den Misserfolg einer Konzeption, aber helfen über das potentiell verkürzte Zeitfenster für eine erfolgreiche Konzeption aufzuklären und über die Möglichkeiten einer Infertilitätsbehandlungen aufzuklären.

Assessment of Ovarian Reserve

Tests recommended to assess ovarian reserved (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268–273

Test	Details
FSH (follicle stimulating hormone) plus estradiol	<ul style="list-style-type: none"> • Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation
Anti Müllerian Hormone (AMH)	<ul style="list-style-type: none"> • No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation
Antral follicle count (AFC)	<ul style="list-style-type: none"> • Number of visible follicles (2–10 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.

Kontrazeptive Möglichkeiten für Frauen nach Brustkrebs

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	Oxford / AGO LoE / GR		
➤ 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**