

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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

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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

- ++** 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

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F	5-Fluorouracil
F/U, f.-up	Follow-up
FA 60 C	“US-FAC”: 5-Fluorouracil / <i>doxorubicin 60</i> / cyclophosphamide
FACT-F	Functional Assessment of Cancer Therapy (fatigue scale)
FASG	French Adjuvant Study Group
FDG-PET / CT	(18)F2-fluoro-D-2-desoxyglucose – Positron emission tomography / in combination with computed tomography
FEA	Flat epithelial atypia
FEC	5-Fluorouracil / epirubicin / cyclophosphamide
FEC100	“French FEC”, (“Bonnetterre”): 5-fluorouracil / <i>epirubicin 100</i> / cyclophosphamide
FISH	Fluorescence in situ hybridization
FNA / FNB / FNP	Fine needle aspiration biopsy
FSH	Follicle stimulating hormone
f-TRAM	Free TRAM-Flap
G	Gemcitabine
GABG	German Adjuvant Breast Cancer Group
GCP	Good clinical practice
G-CSF	Granulocyte-colony stimulating factors
GEICAM	Grupo Español de Investigación en Cáncer de Mamma (Spanish Breast Cancer Research Group)
GnRHa	Gonadotropin releasing hormone analogue / agonist
GnRHa + AI	Gonadotropin releasing hormone analogue + aromatase inhibitor
GOS	Goserelin (Zoladex [®])
Gy	Gray
Hand-Foot-Sy.	Hand-foot-syndrome
Hb	Haemoglobine
HDCT	High dose chemotherapy
HER-2	Human epidermal growth factor receptor
high-dose / AST	High-dose chemotherapy with autologous stem cell transplantation
HIP	Health insurance plan
HR	(Steroid) hormone receptor
HRT	Hormone replacement therapy

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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

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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

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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.**
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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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START

Options for Primary Prevention: Modifiable Lifestyle Factors

Prevention

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Gerber / Thomssen
- **Versions 2012–15:**
Dall / Diel / Gerber / Maass / Mundhenke
- **Version 2016:**
Dall / Maass

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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)**
 - So far, there is no evidence for a correlation between aluminium containing antiperspirants and breast cancer
 - So far, there is no evidence for Glyphosate herbicide use and breast cancer

High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors

population attributable fractions (PAFs) of modifiable risk factors

Risk factors: obesity, physical inactivity, alcohol, low-fibre intake, smoking

Results: retrospective cohort study (Netherlands Cancer Registry)

2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.

2010: breast cancer incidence as compared to background incidence in these subgroups

25.7 % of postmenopausal breast cancer cases in the Netherlands in 2010 are attributable to lifestyle factors

8.8% for obesity

6.6% for alcohol

5.5% for physical inactivity

3.2.% for low fibre intake

4.6% for smoking

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Further
Information

References

Secondary Prevention, Lifestyle and TNBC Subgroup

TNBC subgroup:

N = 518 pat., population-based prospective cohort study, FU 9.1 yrs.

factor: risk of recurrence

phys. activity HR 0.58 (0.39-0.86)

BMI no differences

Bao et al., Epidemiology 2015, 26:909-16

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Secondary Prevention, Lifestyle and ER-positive Subgroup

ER-positive subgroup:

n = 6295 pat., prospective pooling study, 5 yrs. after Dx

no weight gain	HR 1.00
≥ 10% weight gain	HR 1.24 (1.00-1.53)
BMI 30-34.99	HR 1.40 (1.05-1.86)
BMI >35	HR 1.41 (1.02-1.62)
no alcohol	HR 1.00
daily alcohol	HR 1.28 (1.091-1.62)
phys. activity	
none	HR 1.00
< 17.4 MET-h/wk	HR 0.81 (0.71-0.93)
≥ 17.4 MET-h/wk	HR 0.71 (0.61-0.82)

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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) | 2a | B | ++ |
| ➤ Premenopausal | 3a | B | ++ |
| ➤ Postmenopausal | 2a | B | ++ |
| ➤ Prevention/Screening and treatment
of diabetes mellitus type II
(reduction of breast cancer incidence
and mortality) | 2b | B | ++ |

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Prevention by Changing Lifestyle

Factors: Diet

Oxford / AGO
LoE / GR

➤ Preference of a healthy diet

2b B +

➤ Dietary components

➤ Fat reduced food (unsaturated > saturated fatty acids)

2a B +

➤ Reduced consumption of red meat

2a B +

➤ Supplementation of vitamins, minerals, tracer elements

2a B -

➤ Vitamin D substitution for prevention

3a B +/-

➤ Vegetables / fruits

2a B +/-*

➤ Phytoestrogens / soya

2a B +/-

➤ Fiber containing food

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**
- **Invasive lobular tumors**

2b B

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)**
- **Young women smoking have a 60% increased risk of bc, when smoking > 10 years before the first childbirth (vs. never smokers)**

2a B ++

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

Oxford / AGO

LoE / GR

➤ Physical exercise

2a⁽⁻⁾ B ++

(Metabolic equivalents to 3–5 hrs
moderate pace walking per week)

Prevention by Modifying Lifestyle Risk Factors: Hormone Therapy in Postmenopausal Women

Oxford / AGO
LoE / GR

- **Avoiding hormonal therapy in postmenopausal women**
 - **Avoiding estrogen / progestin combinations**
 - **Avoiding estrogens only**

1b A +

1b A +/-

Prevention

Hormones in Postmenopausal Patients

	N	MC-RR(95%CI)	Further information
WHI WHI: JAMA 2002	~ 27 000	1.3 (1,0-1,6)	1,3 (1.1-1,6) coronaric events 1,4 (1,1-1,9) insults 2,1 (1,4-3,3) pulmonary embolism 2,1 (1,5-2,9) deep vein thrombosis
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. age 67 J no secondary prevention side effects as comp. to WHI + cholecystectomy ⁷
Million Women Beral V: Lancet 2003	1.084 110 ~ 50% HRT 4.1 J. follow-up	1.66 (1.6-1.8)	EPC > E mode of applic. not relevant duration > 5 yrs. 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	side effects as compared to WHI +

Chlebowski et al., Climacteric 2015, 18:336-8

Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24

Prevention

Hormones (EGC) in Postmenopausal Patients

	N	MC-RR(95%CI)	Further statements
CLEAR-study (NSW)	1236 BC cases	2.09 (1,57-2.78)	current user
Case-Control-Study, retrospect. Australia		1.03 (0.82-1.28)	past user
		2.62 (1.56-4.38)	E/P combination
		1.80 (1.21-2.68)	E only

Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

Oxford

LoE

1a

- Overall, OC does not significantly increase risk of cancer
- Risk of breast cancer may be slightly increased, risk of ovarian, endometrial cancer is decreased

1a⁽⁻⁾

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Further
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Options for Primary Prevention: Modifiable Lifestyle Factors (2/17)

Further information and references:

Screened data bases:

Pubmed 2005 - 2015, ASCO 2012 – 2015, SABCS 2012 – 2015, Cochrane data base (2014)

Screened guidelines:

NCI (National Cancer Institute , 2015): <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2015)

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

CMA (Canadian Medical Association , 2015): <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

NCCN (National Comprehensive Cancer Network , 2015):

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

Non Modifiable Risk Factors for Breast Cancer (3/17)

No further information

References:

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Modifiable Risk Factors for Breast Cancer Risk (4/17)

No further information

References:

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High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors (5/17)

No further information

No references:

Secondary Prevention, Lifestyle and TNBC Subgroup (6/17)

No further information

No references

Secondary Prevention, Lifestyle and ER-positive Subgroup (7/17)

No further information

No references

Prevention by Changing Pregnancy Related Factors (8/17)

No further information

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Prevention by Changing Life Style Factors: Body Mass Index / Diet (9/17)

No further information

References:

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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.
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Prevention by Changing Life Style Factors: Diet (10/17)

No further information

References:

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Prevention by Modifying Life Style Risk Factors: Alcohol (11/17)

No further information

References:

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Prevention by Modifying Life Style Risk Factors: Smoking (12/17)

No further information

References:

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Prevention by Modifying Life Style Risk Factors: Physical Activity (13/17)

No further information

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Prevention by Modifying Life Style Risk Factors: Hormone Therapy in Postmenopausal Women (14/17)

No further information

References:

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11. Salagame et al., Int J Cancer 2015. DOI 10.1002 Epub ahead of print

Prevention - Hormones in Postmenopausal Patients (15/17)

No further information

No references

Prevention - Hormones (EGC) in Postmenopausal Patients (16/17)

No further information

No references

Prevention by Modifying Life Style Risk Factors: Oral contraception (17/17)

No further information

References:

1. Cibula D.:Hormonal contraception and risk of cancer. Human Reproduction Update, Vol.16, No.6 pp. 631–650, 2010
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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Risk and Prevention

Breast Cancer Risk and Prevention

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➤ Versions 2003–2015:

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

➤ Version 2016:

Schmutzler / Stickeler

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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: ++

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**

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate $\geq 10\%$ in ~25.000 families tested by 2015

Suggested Use of a Screening Checklist *

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8350379533 Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust-und/oder Eierstockkrebs (Mamma-Ca incl. DCIS)

Name der Patientin: _____ Geburtsdatum: ____/____/____

A. Patientin oder Patient und deren Eltern/Geschwister/Kinder	ggf. Anzahl (Bitte ankreuzen)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei der Patientin vor dem 36. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei der Patientin vor dem 51. LJ	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei der Patientin, das erste vor dem 51. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin nach dem 50. LJ	<input type="checkbox"/> 1	1	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei der Patientin	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines uni- oder bilateralen Mammakarzinoms bei einem Patienten (inkl.)	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei Brüdern/Söhnen/Vätern/Neffen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms/primären Peritonealkarzinose bei Schwestern/Töchtern/Müttern/Nichten	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe Patientin und deren Eltern/Geschwister/Kinder	A <input type="text"/>		
B. Weitere mütterliche Linie	Anzahl (Bitte ankreuzen)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere mütterliche Linie	B <input type="text"/>		
C. weitere väterliche Linie	Anzahl (Bitte ankreuzen)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere väterliche Linie	C <input type="text"/>		
D. Der höhere Wert aus B und C	D <input type="text"/>		
E. Summe aus A und D = Risiko-Score	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> >7 A+D <input type="text"/>		

Version 06. Januar 2016 (© Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs)

Formular design: BKKL, Hübner, Version 2.1

Schutzlärk20Auftrag20164.pdf

*online tool provided by the Ärztekammer Westfalen-Lippe in cooperation with the GC-HBOC based on the inclusion criteria of the GC-HBOC, http://www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/FB-erbliche_Belastung_V2016-01-06.pdf

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**

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Mutation Prevalences in TNBC

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Information

References

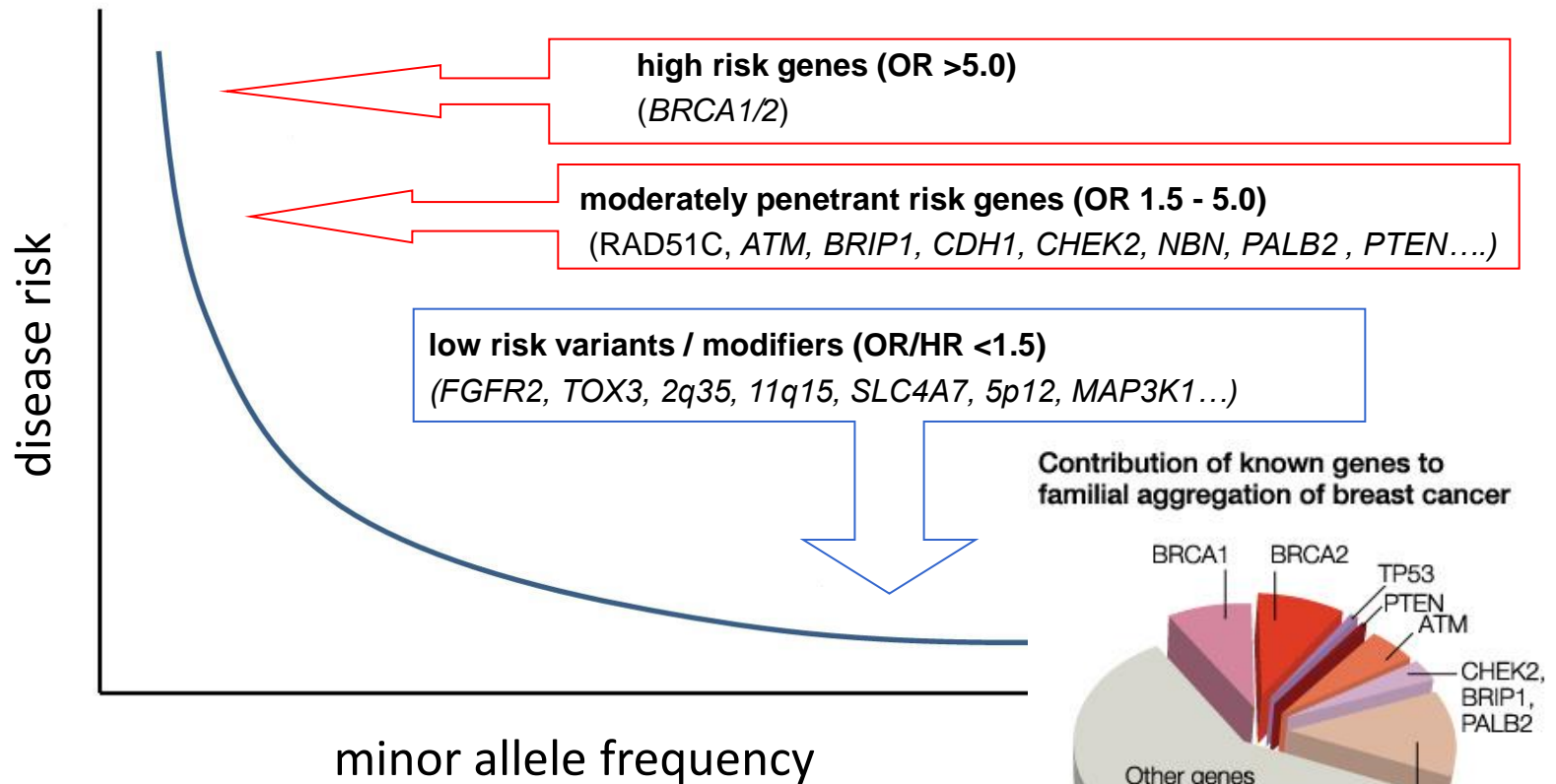
	<35 y	35-39 y	40-49 y	50-59 y	>=60 y	Total
No BC, no OC	18/91 (23%)	23/149 (15.4%)	18/209 (8.6%)	18/241 (7.5%)	6/279 (1.4%)	83/969 (8.5%)
1 BC, no OC	7/48 (14.6%)	7/50 (14%)	14/103 (13.6%)	5/80 (6.3%)	4/79 (5.1%)	37/360 (10.3%)
>=2 BC, no OC	6/12 (50%)	6/16 (37.5%)	8/38 (21%)	2/28 (7.1%)	1/23 (0%)	23/117 (19.7%)
>= 1 OC	3/5 (60%)	8/15 (53.3%)	7/18 (38.9%)	10/17 (58.8%)	1/7 (14.3%)	29/62 (46.8%)
Total	34/156 (21.8%)	44/230 (19.1%)	47/368 (12.8%)	35/366 (9.6%)	12/388 (3.1%)	173/1508 (11%)

State of the Art

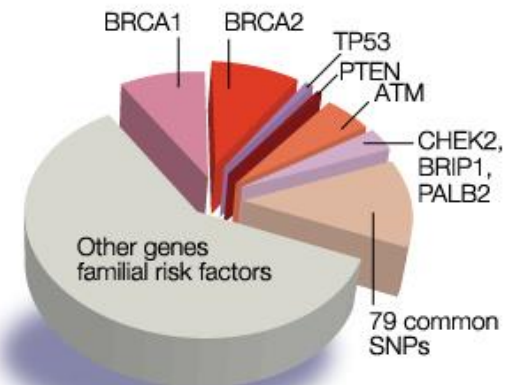
Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

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Contribution of known genes to familial aggregation of breast cancer



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Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer

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 %
Ataxia telangiectasia (AT-Syndrome)	ATM	20-40 % ⁶
Franconi Anämie	RAD51C / D PALB2	Ovary: ~ 10 % ^{7,8} > 30 % ⁹
Nijmegen-Breakage Syndrome	NBN	20-30 % ^{10,11} for slavic founder mutation 657del5

Recommendation: genetic counselling: GCP

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	candidate #1	candidate #2
candidate #3	candidate #4	candidate #5	candidate #6	candidate #7	candidate #8	candidate #9	candidate #10
candidate #11	candidate #12	Candidate #13	Candidate #14	Candidate #15	Candidate #16	Candidate #17	candidate #18
candidate #19	candidate #20						

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)
- 20 BC/OC 'research genes'**

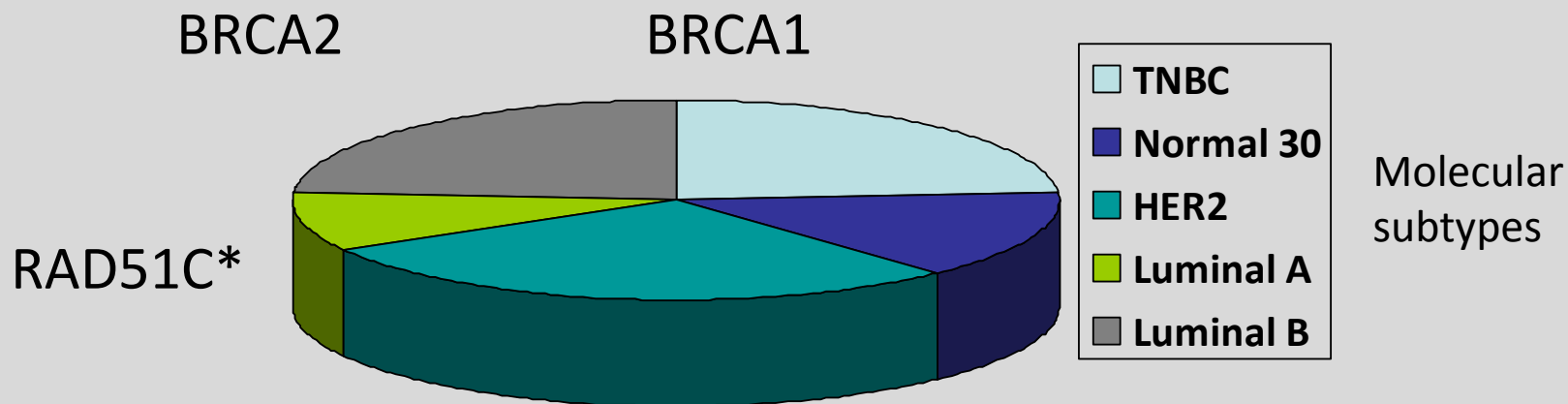
Strategy:

- 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. 2013

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

Genetically Defined Subtypes are Distinct Tumor Entities

- Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:
- 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
- Classification of sequence variants should be performed according to the IARC classification system
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet

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References

Variant classification proposed by IARC (Plon et al., Human Mutation, 2008)

Proposed Classification System for Sequence Variants Identified
by Genetic Testing

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

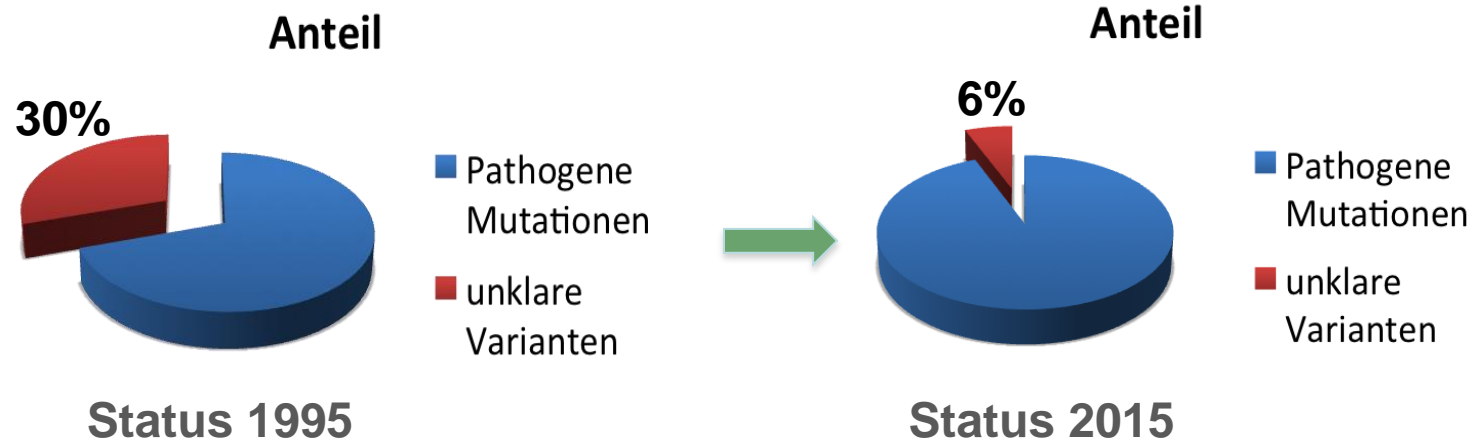
Only class 4 and 5 variants are considered clinically relevant

Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.

- Co-occurrence data from large data banks
- Segregation analysis
- Functional analysis etc.

To be accumulated by large study groups such as ENIGMA



Improvement of IARC class 3 classification in the German population by GC-HBOC

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing*

- 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 valide 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

Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health

<http://www.bmg.bund.de/themen/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/querschnittsthema-risiko-adaptierte-krebsfrueherkennung.html>

Current Clinical Impact of non-BRCA1/2 Breast Cancer Risk (NBBC) Genes

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

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

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

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

- 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

Oxford / AGO
LoE / GR

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

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References

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Non Directive Counseling for the Uptake of Preventive Measures

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GCP C ++

- 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)**

Oxford / AGO LoE / GR

1a A ++

2b B +

2a B ++

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Further
Information

References

Surveillance Program for Female Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC*

**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)			3	B	+

***Referral to centres of the GC-HBOC or cooperating centres is recommended**

MRI Breast Screening in High-risk Women

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MRI breast screening in high-risk women: cancer detection and survival analysis. Evans DG, Kesavan N, Lim Y, Gadde S, Hurley E, Massat NJ, Maxwell AJ, Ingham S, Eeles R, Leach MO, MARIBS Group, Howell A, Duffy SW. Breast Cancer Res Treat. 2014 Jun;145(3):663-72. doi: 10.1007/s10549-014-2931-9. Epub 2014 Apr 1.

**See Table 4: Five- and 10-year overall survival in BRCA women and
Figure 1: overall survival in BRCA women**

Further
Information

References

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Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC*

**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**

Surveillance for Male Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC*

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BRCA1 mutation carrier have a near average life time risk to develop breast cancer and a 1.8-4.5-fold risk to develop prostate cancer by $\leq 65y$.

BRCA2 mutation carrier have a 5-7% life time risk to develop breast cancer and a 2.5-8.6-fold risk to develop prostate cancer by $\leq 65y$.

**Oxford / AGO
LoE / GR**

Currently no specific surveillance is recommended

- **For breast cancer prevention:
self examination and watchful waiting**
- **For prostate cancer prevention:
study participation if available**

5 D +

3b C +

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Further
Information

References

Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

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

Surgical Prevention

Oxford / AGO
LoE / GR

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

2a

B +*

Surgical Prevention for Healthy Female BRCA1/2 Mutation Carriers

Oxford / AGO
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
- **Contralateral 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 Female Mutation Carriers Affected by Breast Cancer

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- | | 2b | B | + |
|--|----|---|------|
| ➤ 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 | ++* |
| ➤ Contralateral 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 | 2a | B | +++* |

+ Overall prognosis has to be considered

*Study participation recommended

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in BRCA1/2 Mutation Carriers

Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Heemskerk-Gerritsen BA1, Rookus MA, Aalfs CM, Ausems MG, Collée JM, Jansen L, Kets CM, Keymeulen KB, Koppert LB, Meijers-Heijboer HE, Mooij TM, Tollenaar RA, Vasen HF; HEBON, Hooning MJ, Seynaeve C.

Int J Cancer. 2015 Feb 1;136(3):668-77. doi: 10.1002/ijc.29032. Epub 2014 Jul 8.

See table 3: Efficacy of contralateral risk-reducing mastectomy on overall survival

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.

Therapy of BRCA1/2-associated Breast Cancer+

Limited prospective cohort studies with short follow-up time

	Oxford / AGO LoE / GR		
➤ Breast conserving therapy:			
➤ Adequate local tumor control (10 years observation)	2a	B	+
➤ Systemic therapy according to sporadic breast cancer	3a	B	+
➤ BRCA1/2 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

BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto

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Rezai, Bernd Gerber, Serban Dan Costa, Jens-Uwe Blohmer,
Tanja Fehm, Jens Huober, Cornelia Liedtke, Volkmar Müller,
Valentina Nekljudova, Karsten E Weber, Brigitte Rack,
Matthias Rübner, Liewei Wang, James N Ingle,
Richard M Weinshilboum, Gunter von Minckwitz and Fergus
Couch**

**for the
GBG/AGO-B study groups**

Further
Information

References

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Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)

Gunter von Minckwitz, Sibylle Loibl, Andreas Schneeweiss, Christoph Salat, Eric Hahnen, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens Uwe Blohmer, Hans Tesch, Fariba Khandan, Peter Fasching, Christian Jackisch, Rita Schmutzler, Valentina Nekljudova, Michael Untch

**for the
GBG/AGO-B study groups**

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Medical Prevention for Women at Increased Risk

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- **Tamoxifen for women > 35 years**
Reduction of invasive BrCA, DCIS, and LN
- **Raloxifen for postmenopausal women**
Reduction of invasive BrCa only
- **AI for postmenopausal women**

1a A +*

1b A +*

1b A +[#]

#Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers
Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

***Risk situation as defined in NSABP P1-trial (1.66% in 5 years)**

Risk Reduction for Ipsi- and Contralateral Breast Cancer

Rationale: Women with breast cancer have an increased risk for a second primary

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|----------|
| ➤ Tamoxifen* | 1a | A | + |
| ➤ Aromatase inhibitors* | 1a | A | + |
| ➤ Suppression of ovarian function*
+ Tamoxifen | 1b | B | + |

***Only proven for ER/PgR-positive primary sporadic BrCa**

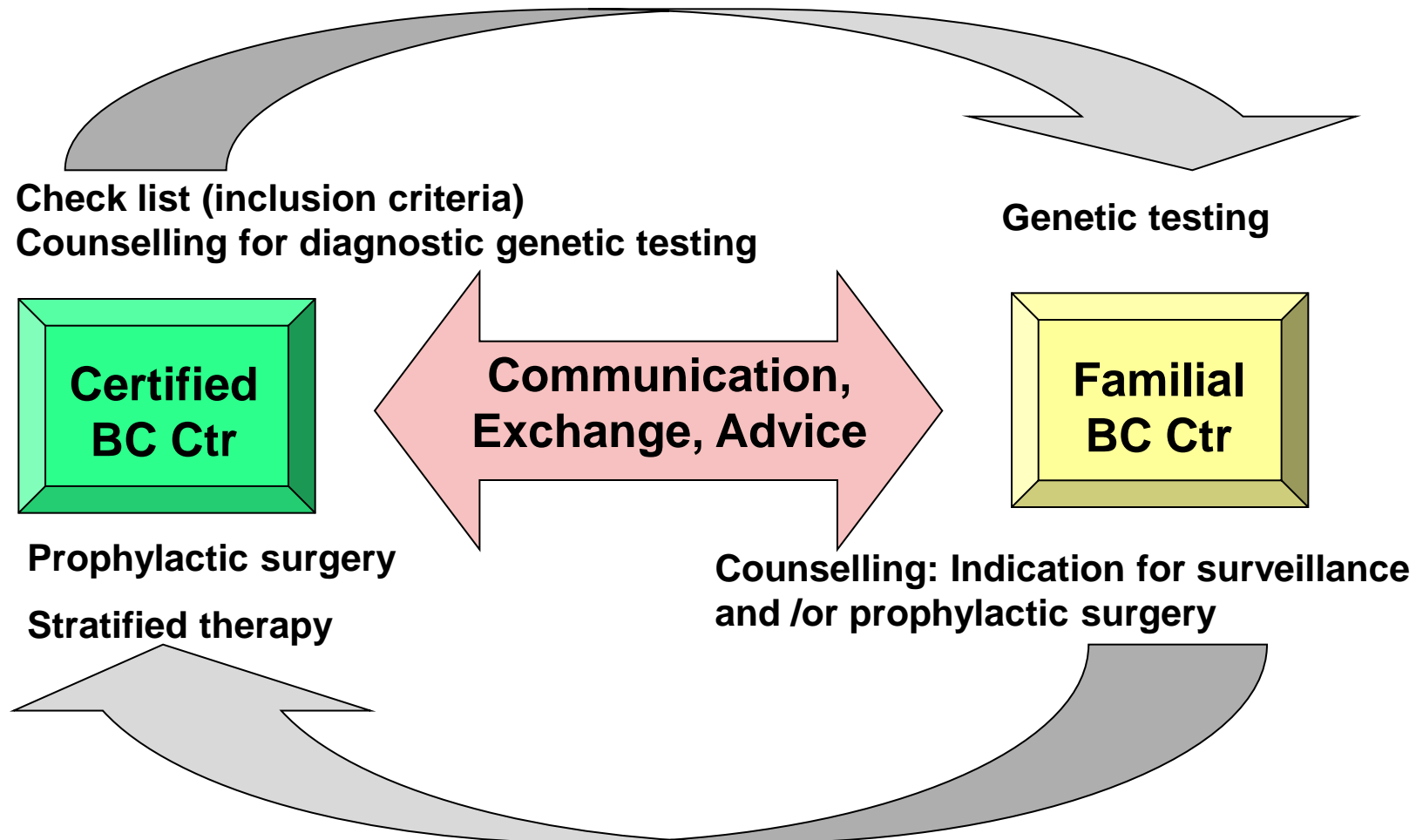
Further
Information

References

Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

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References

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* trans-sectoral contract for integrated care, acc. to code of social law
§ 140a since 2015

Breast Cancer Risk and Prevention (2/35)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references

Principles in Prevention (3/35)

No further information

No references

Who Should be Tested for BRCA1/2 Mutations? (4/35)

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%.

Suggested Use of a Screening Checklist (5/35)

No further information

No references

BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (6/35)

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 JI, 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.
2. Sanford RA1, Song J2, Gutierrez-Barrera AM3, Profato J4, Woodson A4, Litton JK3, Bedrosian I5, Albarracin CT6, Valero V3, Arun B3. High incidence of germline BRCA mutation in patients with ER low-positive/PR low-positive/HER-2 neu negative tumors. Cancer. 2015 Oct 1;121(19):3422-7. doi: 10.1002/cncr.29572. Epub 2015 Aug 17.

3. Robertson L, Hanson H, Seal S, Warren-Perry M, Hughes D, Howell I, Turnbull C, Houlston R, Shanley S, Butler S, Evans DG, Ross G, Eccles D, Tutt A, Rahman N; TNT Trial TMG; BCSC (UK). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. *Br J Cancer*. 2012 Mar 13;106(6):1234-8. doi: 10.1038/bjc.2012.31. Epub 2012 Feb 14.

Mutation prevalences in TNBC (7/35)

Further information:

W/o fam. history and cumulative up to 50 y: 13%

References:

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No further information

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Clinical Implication:Genotype/Phenotype (12/35)

No further information

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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)

MRI Breast Screening in high-risk women (22/35)

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Prophylactic bilateral salpingo-oophorectomy (BSO) 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 BSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after BSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, BSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend BSO in mutation carriers after completion of childbearing around the age of 40.

Prophylactic bilateral mastectomy (BIM) 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 BSO (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 (28/35)

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Improved survival after contralateral risk-reducing mastectomy (29/35)

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Therapy of BRCA1/2-associated Breast Cancer+ (30/35)

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TED poll:

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

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At present, the German consortium for hereditary breast and ovarian cancer recommends surgical and adjuvant therapy of hereditary breast cancer according to standard guidelines.

As the risk of contra-lateral breast cancer is 30- 40% in 10 years while the risk of ipsi-lateral breast cancer is not significantly elevated (Metcalf et al. JCO 2004, Pierce L. et al. JCO 2006), cl-MXT may be considered.

PBSO significantly reduces the risk of ovarian cancer from 12.7% to 6.8% in 10 years (p=0.03) in breast cancer affected women. Therefore, PBSO is recommended in case of a good prognosis i.e. stage I breast cancer (Metcalf K. et al. *Gynecol Oncol* 2005).

BRCA1 associated breast cancers have a poor prognosis that is mitigated by adjuvant chemotherapy (Robson et al. *Breast Cancer Res* 2003). Moreover, in vitro studies suggest a distinct chemosensitivity profile of BRCA associated breast carcinomas (Lafarge et al. *Oncogene* 2001, Quinn et al. *Cancer Res* 2003). Recent data suggest the benefit of new

therapeutic strategies that need to be further proven by RCTs. Therefore, affected BRCA mutation carriers and women at high risk should be referred to the centres for familial breast and ovarian cancer

BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto Study (31/35)

No further information

No references

Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto) (32/35)

No further information

No references

Medical Prevention for Women at Increased Risk (33/35)

No further information

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Risk Reduction for Ipsi- and Contralateral Breast Cancer (34/35)

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

Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (35/35)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Early Detection and Diagnosis

Early Detection and Diagnosis

- **Versions 2005–2015:**
**Albert / Blohmer / Fersis / Junkermann /
Maass / Scharl / Schreer**
- **Version 2016:**
Schreer / Albert

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

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* National Mammography-Screening-Program

Breast Cancer Mortality Reduction

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Meta-Analyses

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)

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Meta-Analyses

RR (95%CI)

Case-Control Studies

Broeders et al	Screening Mx	0.46 (0.4 – 0.54)
	Corr. for self selection	0.52 (0.42-0.65)
	Invited for screening	0.69 (0.57-0.83)

Incidence-based Mortality Studies

Broeders et al	Screening Mx	0.62 (0.56-0.69)
	Invited to screening	0.75 (0.69-0.81)

Randomized Clinical Trials

Gotsche and Jorgenson	Screening Mx	0.81 (0.74-0.87)
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Breast Cancer Mortality Reduction

Age Group (yrs)	NNS	
	Mortality Reduction 20%	40%
40 - 49	1770	753
50 - 59	1087	462
60 - 69	835	355

4 systematic reviews of 8 RCTs,
1 systematic review of 7 cohort studies and metaanalysis of case-control studies

Breast Cancer Screening

ACS Guideline Update 2015

American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age.

The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

Recommendations

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)

1a. Women aged 45 to 54 years should be screened annually. (*Qualified Recommendation*)

1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. (*Qualified Recommendation*)

1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (*Qualified Recommendation*)

2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. (*Qualified Recommendation*)

3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. (*Qualified Recommendation*)

^aA strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.¹

Breast-Cancer Screening- Viewpoint of the IARC Working Group

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Method	Strength of Evidence
Reduces breast-cancer mortality in women 50-69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70-74 yr of age	Sufficient
Reduces breast-cancer mortality in women 40-44 yr of age	Limited
Reduces breast-cancer mortality in women 45-49 yr of age	Limited
Detects breast cancer that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50-74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50-69 yr of age who are invited to attend organized mammographic screening programs	Sufficient

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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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**
- **Second-look US (MRI-only detected lesions)**

2b B ++
2b C ++

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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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* May increase breast awareness

Assessment of Breast Symptoms or Lesions

	Oxford / LOE / GR	AGO
➤ Clinical examination	3b	B ++
➤ Mammography	1b	A ++
➤ Additional Tomosynthesis (vs spot compression)	2b	B +
➤ Sonography	2b	B ++
➤ Elastography (shear-wave)	2a	B +
➤ Automated 3D-sonography	3b	B +/-
➤ MRI*	2b	B +/-
➤ Minimally invasive biopsy	1c	A ++

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

Pretherapeutic Assessment and Staging

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	Oxford / LOE / GR	AGO
➤ Clinical examination	5 D	++
➤ Mammography	2b B	++
➤ Mammography + Tomosyntheses + Sonography added MRI	3b B 3b 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

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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)]**

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

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

N Houssami et al. Ann Surg 2013; 257

MRI Scceening (High-risk) Benefit

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- **Early detection of cancer cases additionally to conventional imaging**
- **Improved patient prognosis?
(Mortality reduction? Reduction of interval cancers?)**

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MRI Screening 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	-

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

False-positive MRI

3,43–4,86

Benign biopsies

1,22–9,50

**Benign surgical biopsies
(MARIBS)**

2

False-negative MRI (MRISC)

22%

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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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References

Early Detection and diagnosis (2/19)

Further information and references:

Screened data bases:

- Pubmed 2013 - 2015
- Medline 2013 – 2015
- Cochrane 2013 - 2015

Guidelines:

- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge
- 2015 ACS Update Breast Cancer Screening for women at average risk
- IARC Handbook 2016

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

Early Detection – Mammography (3/19)

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 38-48% 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 - 2009) showed an marked increase in early-stage breast cancer (DCIS and localised breast cancer) and a reduction of late-stage cancer of 37% compared with the prescreen trends.

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 (4/19)

No further information

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Breast Cancer Mortality Reduction (5/19)

No further information

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Breast Cancer Mortality Reduction (6/19)

No further information

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2015 Guideline Update From The American Cancer Society (7/19)

No further information

No further references

Breast cancer screening – Viewpoint of the IARC Working Group (8/19)

No further information

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Mammography Screening Women 40–49 years (9/19)

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 was too short for this young age group. Recently a significant reduction in breast cancer mortality in the first 10 years after diagnosis as noted in the intervention group compared with the control group (RR 0.75, CI 0.58-0.97), but not thereafter. 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 (10/19)

Further information:

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.

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 recall and biopsy rate. Supplemental ultrasound is associated with increasing costs. Modeling suggests for women between the ages of 50 and 74 years with heterogeneously or extremely dense breast tissue may avert only 0.4 breast cancer deaths but result in 354 additional biopsy recommendations per 1000 women screened compared with biennial screening mammography alone, with a cost-effectiveness ratio of \$325 000 per quality-adjusted life-year gained (Sprague BL, et al 2015).

Automated ultrasound (ABUS/AVUS) might overcome the time-consuming and costly nature of hand-held, physician-performed whole-breast ultrasound but data are immature (accuracy cohort studies only).

The IARC Working Group statement on ultrasound as an adjunct to mammography in women with dense breasts and negative results on mammography are: Inadequate evidence concerning breast cancer mortality reduction, limited evidence for breast cancer detection rate, inadequate evidence for a reduction of the interval cancer rate and sufficient evidence for an increase of FPs. This is in line with the recommendations of the U.S. Preventive Services Task Force (Siu A 2016).

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Early Detection Clinical Examination (11/19)

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.

The ACS updated Guideline 2015 does not recommend clinical breast examination for breast cancer screening among average-risk women at any age.

The IARC Working Group states that there is inadequate evidence for a reduction of breast cancer mortality.

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Assessment of Breast Symptoms or Lesions (12/19)

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 (DBT) in the diagnostic setting (specifically, evaluation of mammographic abnormalities) has been shown to be at least as effective as spot compression views for workup of noncalcified abnormalities, including asymmetries and distortions. For DBT combined with 2-view full-field digital mammography (FFDM) radiation doses are elevated, at a maximum by a factor $\sim 2 \frac{1}{4}$ of that for FFDM alone. A replacement of FFDM with synthetic 2D-views reduces the breast dose approximately by half. Problems to be solved concern additional reading time, IT storage, overdiagnosis and cost effectiveness (Gilbert FJ, et al 2015).

Shear wave elastography (SWE) is a promising adjunct to greyscale ultrasound in differentiating benign from malignant breast masses adding 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. A systematic review and metaanalysis using shear-wave elastography combined with conventional ultrasound resulted in a sensitivity of 0.971 (95% CI 0.941-0.986) and specificity of 0.801 (95% CI 0.733-0.856) (Liu B, 2015).

Accuracy studies demonstrate that automated ultrasound (ABUS/AVUS) is a potentially feasible way to overcome limitations of hand-held breast ultrasound such as operator dependence and non-reproducibility.

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 (13/19)

Further information:

Sonography corresponds better than mammography with the pathological tumour 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 tumours, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment.

A recent prospective study examined the accuracy of digital breast tomosynthesis (DBT) and magnetic resonance imaging (MRI) added to digital mammography (DM) and ultrasound (US) in the preoperative assessment of breast cancer. DBT had higher sensitivity than DM (90.7% vs. 85.2%). Combined DM and DBT with US yielded a 97.7% sensitivity; despite high sensitivity of MRI (98.8%), the addition of MRI to combined DM with DBT and US did not significantly improve sensitivity. Overall accuracy did not significantly differ between MRI and DM with DBT and US (92.3% vs. 93.7%). Breast density affected sensitivity of DM and DBT (statistically significant difference for DM), not MRI. The authors concluded that there is little gain in sensitivity and no gain in overall accuracy, by performing MRI for patients who have been evaluated with DM with DBT and US (Mariscotti G et al 2014).

Axillary ultrasound is recommended for pretherapeutic assessment to guide axillary surgery (Feng Y et al 2015). 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.

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 both invasive and non-invasive cancer.

In case of large areas of highly suspicious microcalcifications on mammography several percutaneous biopsies to define tumour size should be performed before deciding upon mastectomy.

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MRI: Preoperative Staging (14/19)

No further information

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MRI Preoperative Staging in Lobular Invasive Breast Cancer (15/19)

No further information

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MRI Screening (High-risk) – Benefit (16/19)

No further information

No references

MRI Screening in Women with High Familial Risk (17/19)

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 (18/19)

No further information

No references

MRI and DCIS (19/19)

No further information

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Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Pathology

Pathology

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- **Version 2016:**
Blohmer / Kreipe

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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**

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5 D ++

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Use of Fine Needle Aspiration Cytology*

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

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5	D	+/-
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5	D	+/-
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* **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)

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

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5 D ++

1b B ++

5 D - -

3b C ++

5 D +

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Workup: Breast-Conserving Specimens

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➤ 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.

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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References

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
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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

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	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 tumor cannot be
assessed (e.g. tumor in multiple specimens)**

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Reporting: Lymphovascular Invasion

Oxford
LoE / GR

AGO

- **L1: Lymphovascular invasion**
L0: No lymphovascular invasion
- **IHC for evaluation of lymphovascular invasion**
- **Differentiation of peritumoral and extensive lymphovascular invasion**
- **Reporting of venous invasion (V0/V1) optional, prognostic significance not established**

5 D ++

3b C -

3b C ++

5 D +

Further
Information

References

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 not at the invasion front

Do not consider central fibrosis and necrotic areas

Report average of lymphocytic infiltrate as percentage

*Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruner, 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
➤ 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 $\geq 10\%$, low pos. if $\geq 1\%$ -9%)	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	+

**For therapeutic implications see chapter
“Endocrine therapy”**

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Special Studies: PgR-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 $\geq 10\%$)	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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References

Additional Special Studies: Molecular Analysis of ER/PgR Status

Oxford / AGO
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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LoE / GR

1a A ++

- **Reporting of immunohistochemistry (IHC):**
 - HER2+ if strong complete circular membrane staining of > 10% invasive cells (3+ staining pattern)
 - if > 10% circular but moderate/weak membrane staining or ≤ 10% strong staining, U-shaped staining in micropapillary carcinoma (2+ staining pattern): ISH required (CISH, SISH, FISH)

- **Reporting of single-color In-Situ-Hybridisation (ISH):**
 - HER2+ if signal counts ≥6 in at least 20 cohesive cells, negative if signal counts < 4 signals/nucleus

3a C ++

- **Reporting of dual-color ISH:**
 - positive if signal ratio HER2:CEP17 ≥ 2,0 and/or HER2-signals ≥6

3a C ++

- **Equivocal results (2+ IHC, ≥4 - <6 HER2 signals ISH):** Retest using other method and/or tissue block

3a C ++

- **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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➤ 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-Type, 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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References

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: $15\% \pm 5\%$**
- **Use of standardised 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
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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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8. Royal College of Pathologists (UK) (2005). NHSBSP guidelines for pathology reporting in breast disease.
<http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html>
9. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8

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:

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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

1. Heywang-Köbrunner SH, Sinnatamby R, Lebeau A, Lebrecht A, Britton PD, Schreer I; Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): results of a European consensus meeting. Eur J Radiol. 2009 Nov;72(2):289-94

Statement: Frozen section diagnosis on core biopsies

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

1. Harris G, Denley H, Pinder S et al. Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. Am J Surg Pathol 2003; 27: 11-15.
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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:

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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.
2. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8
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Workup: Sentinel Node Biopsy (10/30)

No further information

References:

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

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
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

1. Brown, NM, TT Stenzel, PN Friedman, J Henslee, G Huper, and JR Marks. "Evaluation of Expression Based Markers for the Detection of Breast Cancer Cells.." *Breast Cancer Research : BCR* 97, no. 1 (April 30, 2006): 41–47.
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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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Reporting: Grade of Malignancy (13/30)

No further information

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Reporting: Lymphovascular invasion (17/30)

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Reporting: Evaluation after Neoadjuvant Chemotherapy (19/30)

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Special studies: ER-Testing by IHC (20/30)

No further information

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Special studies: PgR-Testing by IHC (21/30)

No further information

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Additional special studies: Molecular analysis of ER/PgR status (22/30)

No further information

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Special studies: HER2 Testing (23/30)

No further information

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HER2 Testing on Core Biopsies (24/30)

No further information

No references

Additional special studies: Molecular analysis of HER2 Status (25/30)

No further information

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No further information

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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

- **Versions 2002–2015:**
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Göhring / Harbeck / Janni / Liedtke / Loibl /
Mundhenke / Nitz / Rody / Schaller /
Schmidt / Schmutzler / Schneeweiss /
Simon / Solomayer / Thomssen**
- **Version 2016:**
Witzel / Nitz

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
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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

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

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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 >30 kg/m ²)	1b	B	+

* NACT = Neoadjuvant Chemotherapy

Reproducibility

- **ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grading: concordance central vs local is 68 % (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)**
- **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%, in central pathology review (Ann Oncol 2012)**
- **Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)**

Critical Issues Regarding LoEs for Biomarkers

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/ Ki-67 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	+

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[§] 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	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
Prospective- retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%)	ABCSG 6 (19%) ABCSG 8 (36%) GEICAM-9906 (45%) ATAC (10%)	MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%)
Prospective evidence (pending)	MINDACT (completed)	TAILOR _x (N0, low-risk, RS<11) PlanB (N0, high- risk/N+)	-	-

\$ Validated clinical data only available for this assay

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

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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	A	+/-
➤ Therapy decisions based on CTC phenotypes	III	C	-
➤ Multigene assays			
➤ (Oncotype DX®) (N0-/+, HR+ HER2-, 5 Jahre)	I	A	++
➤ (EndoPredict®, Prosigna®) (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 Chemotherapy Response Prediction II

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

^{\$} validated clinical data only available for this assay

*defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front
(lymphocytes make up >50% of stroma area)

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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Further
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\$ Validated clinical data only available for this assay

Prognostic Factors – Metastatic Breast Cancer

Factor

LoE₂₀₀₉

CTS

AGO

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

➤ Prognosis at baseline	I	A	+
➤ Early response assessment (3w)	I	B	+
➤ Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype	I	A	-*

Prognostic and Predictive Factors (2/20)

Further information:

Data bases screened: Pubmed 2008 - 2015, ASCO 2003 – 20015, SABCS 2003 – 2015, Cochrane data base (n.d.)

Guidelines screened:

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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.

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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 low risk tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leucemia / MDS/ other secondary cancers. Because of this, proper risk assessment is mandatory.

Adjuvant chemotherapy reduces breast cancer mortality by one third. Because of this, proper risk assessment is mandatory. In the MINDACT trial for example a group of international experts consented not to propose adjuvant chemotherapy in patients with an estimated distant metastasis free survival of 92% after five years.

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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)

No further information

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Reproducibility (10/20)

Further information:

Conventional pathology and immunohistochemistry is for methodological reasons subject to high inter-observer variability/variable reproducibility. However, comparison of large series in recently conducted trials show high concordance for HR status in central and local pathology, whereas discordances for Ki-67 and grading are clinically meaningful. HER2 discordances in German trials are observed in up to 10% of cases. In the ASCO-CAP guidelines Her2 discordances are reported in up to 6% of cases. In the landmark trials a small number of patients tested HER2negative by IHC derive some benefit from trastuzumab.

For grading a concordance in about 68 % of cases in German trials was seen. MIRROR trialists report upgrading of N0 status by central pathological review in an comparable amount. A high inter- and intraobserver variability in measurement of the proliferation marker ki-67 has been described. Preanalytical and analytical assessment is not standardized. 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)

Further information:

St Gallen Consensus accepted a cut-off for KI-67 of 20%.

Semiquantitative IHC expression of PR (\leq 20%) adds prognostic value with the current IHC based luminal A definition (for cut-off Ki-67 14 %)

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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 into 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. ASCO- guidelines already integrated uPA/PAI1 and Oncotype DX®.

There is new retrospective evidence from the prospective ATAC trial involving 928 patients from the ATAC trial (> 9000 patients) conducted in postmenopausal women (Trans ATAC). In this cohort EP and EP clin were highly prognostic for distant recurrence in endocrine treated patients with ER+/HER2- disease. EPclin provided more prognostic information than RS, particularly after 5 years follow-up and in node positive patients.

In the GEICAM 9906 trial 555 tumors from 1246 patients randomized to receive two different chemotherapy regimens (FEC with or without paclitaxel) between 1999 and 2002 could be analyzed with Endopredict. There were no survival differences for patients with low or high EP Score or EPclin Score with regard to the chemotherapy arms, but the authors state that no event (recurrence) could be observed in the group of patients with low EpClin Score.

In 2015, the first evidence from prospective randomized trials was available for the low-risk group in the TAILOR-X trial (Oncotype Dx) and for the low-/intermediate and high-risk group in the PlanB trial. In the Tailor-X trial a 5 year distant free relapse rate of 99.3% was reported in patients with a low risk situation defined as recurrence score (RS) between 0 and 10. Results refer to 1226 node-negative patients, who received no chemotherapy.

In Plan B according to the inclusion criteria only node negative high risk and node positive candidates for chemotherapy were eligible. 348 (15.3%) patients with RS 0-11 were classified as low risk and did not receive any chemotherapy. 3 year disease-free survival (DFS) in this group was 98%. In the chemotherapy group 3 year DFS was 98% for the RS 12-25 group and 92% for the patients with RS> 25. Results from other prospective trials are pending.

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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. (Ann Oncol 2013) 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)

No further information:

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Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides sample 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, ISH) 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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Further
Information

References

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**

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

B3-Lesions:

~PPV

- | | |
|--|--------|
| ➤ Atypical ductal hyperplasia (ADH) | 20-30% |
| ➤ Lobular intraepithelial neoplasia (LN/LIN) | 0-10% |
| ➤ Flat epithelial atypia (FEA) | 0-10% |
| ➤ Radial scar / Complex sclerosing lesion | 0-10% |
| ➤ Papilloma without atypia | 0-10% |
| ➤ Cellular fibroepithelial tumors / phyllodes tumors | 0% |

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Management after Minimally Invasive Biopsy

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➤ **Interdisciplinary conference: Concordant findings in pathology and imaging?**

→ yes: proceed according to histologic type **3a C ++**

→ no: open biopsy **3a C ++**

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Atypical Ductal Hyperplasia (ADH)

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- Synonyms: Atypical intraductal epithelial proliferation (AIDEP), 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 in Core Biopsy

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ADH in core- / vacuum-assisted biopsy:

- Open excisional biopsy 3a C ++
- Open excisional biopsy may be omitted, with:
 - a) no mass lesion radiologically and
 - b) a small lesion (≤ 2 TDLU* in vacuum biopsy) and
 - c) 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 comedotype necrosis are classified as → **B5a**
- Indicator/Precursor lesion:
Ipsi- and contralateral enhanced breast cancer risk:
7 x at 10 years

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Variants of Lobular Neoplasia

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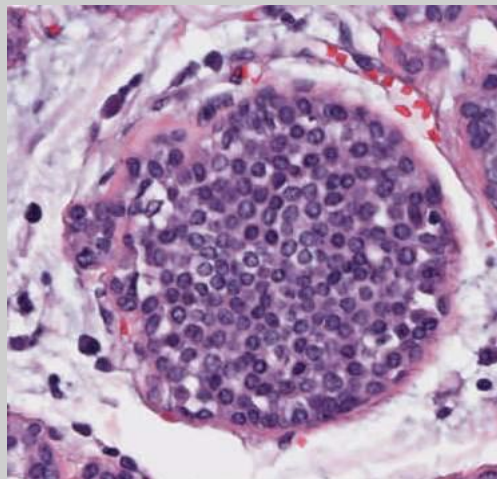
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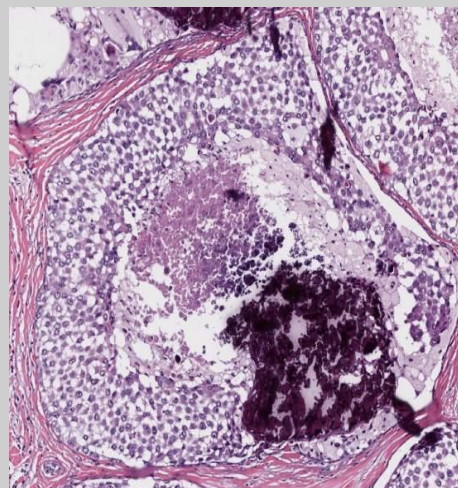
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References

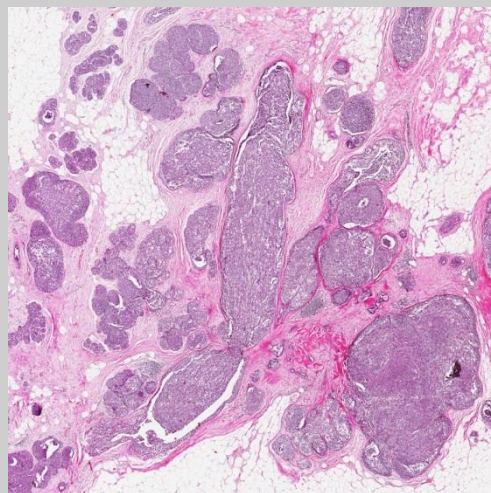
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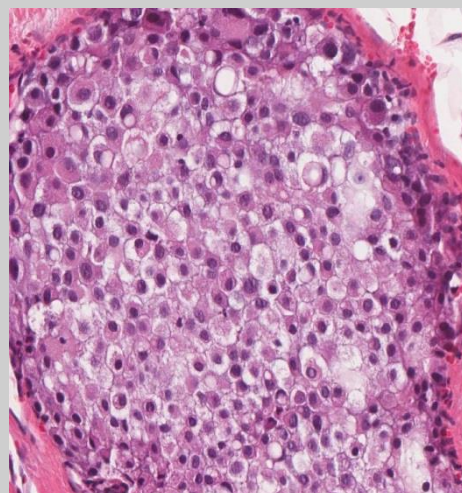
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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	2a	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, histologic step sectioning and correlation with imaging are 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 and peripheral papilloma > 2 mm; atypical intraductal papilloma (B3)
- To be discriminated from peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be discriminated from papilloma with DCIS, from intraductal papillary carcinoma, and from 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 ++

➤ **Multiple papillomas**

→ open biopsy

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

Oxford / AGO
LoE / GR

5 C ++

3a C ++

3a C ++

3a C ++

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

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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.

***Risk situation as defined in NSABP P1-trial (1,66% in 5 years)**

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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
Frakturen	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

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
Gynekological-/ 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

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)

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

Lobular neoplasia (162 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] : "2016/01/01"[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 (78 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] : "2016/01/01"[dp]) AND ("atypical ductal hyperplasia"[ti] OR "atypical hyperplasia"[ti] OR "ADH"[ti]) AND ("english"[la] OR "german"[la])

Flat epithelial atypia (88 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] : "2016/01/01"[dp]) AND ("flat epithelial atypia"[ti] OR "columnar cell"[ti] OR "FEA"[ti]) AND ("english"[la] OR "german"[la])

Papilloma (274 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] : "2016/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[Title]

Radial scar (22 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] : "2016/01/01"[dp]) AND ("radial scar"[ti] OR "complex sclerosing lesion"[ti] OR "radial sclerosing lesion"[ti]) AND ("english"[la] OR "german"[la])

Screened Guidlines:

- 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

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Pathology Reporting for Minimal Invasive Biopsies (3/25)

Further information:

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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).

Current systematic review:

Calhoun, B. C., & Collins, L. C. (2016). Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. *Histopathology*, 68(1), 138–151. <http://doi.org/10.1111/his.12852>

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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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2. Degnim A.: Stratification of breast cancer risk in women with atypia: A Mayo Cohort Study. *JCO* 2007; 25(19):2671-2677
3. Ellis IO: Impact of a national external quality assessment scheme for breast pathology in the UK. *J Clin Pathol.* 2006;59:138-45.
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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:

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

No further information

References:

1. Degnim A, Visscher W, Berman H et al. Stratification of breast cancer risk in women with atypia: A Mayo Cohort Study. JCO 2007; 25(19):2671-2677

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.

References:

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4. Arpino G.: Lobular neoplasia on core-needle biopsy: clinical significance. Cancer 2004, 101:242-250

Statement: Indicator-/ precursor lesion

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Variants of Lobular Neoplasia (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].

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4. Ross DS, Hoda SA. Microinvasive (T1mic) lobular carcinoma of the breast: clinicopathologic profile of 16 cases. *The American journal of surgical pathology.* 2011 May;35(5):750-6.

Strategy after Diagnosis of LIN (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.

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1. Purdie CA et al: Management of in situ lobular neoplasia detected on needle core biopsy of breast. J Clin Pathol. 2010 Nov;63(11):987-93.
2. Moinfar F. Flat ductal intraepithelial neoplasia of the breast: A review of diagnostic criteria, differential diagnoses, molecular-genetic findings, and clinical relevance - It is time to appreciate the Azzopardi concept! Arch Pathol Lab Med 2009; 133(6):879-892.
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Statement: Marker Lesion (LoE 3b)

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4. Collins L: Clinical and pathological features of ductal carcinoma in situ associated with the presence of flat epithelial atypia: an analysis of 543 patients. Modern Pathology 2007; 20:1149-1155
5. Boulos F: Histologic Associations and long-term cancer risk in columnar cell lesions of the breast. Cancer 2008; 113:2415-2421

Strategy after Diagnosis of FEA (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)

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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.

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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.

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Radially Sclerosing Lesion (18/25)

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

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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].

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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
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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

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

No further information

References:

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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.

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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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Ductal Carcinoma in Situ DCIS

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Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

Oxford / AGO
LoE / GR

➤ Mammography	1b	A	++
➤ Magnification view of microcalcification	4	C	++
➤ Increase of <u>detection rate</u> of G1/G2 DCIS by full-field digital mammography (versus screen-film)	2b	B	+
➤ Stereotactic core needle / vacuum biopsy (VAB)	2b	B	++
➤ Specimen radiography	2b	B	++
➤ Marker (Clip) left at biopsy site for location if lesion is completely removed	5	D	++
➤ Assessment of extension			
➤ MRI	3a	C	+/-
➤ Clinical examination	5	D	++
➤ FNA / ductal lavage	5	D	-
➤ Interdisciplinary board presentation	5	D	++

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Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

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- 108.196 patients from the SEER data base
- Retrospective analysis
- Breast cancer specific mortality 3.3 %
- Increased in young women (< 35 years) and black ethnicity
- The risk of death increases after ipsilateral invasive recurrence HR 18 (95%CI, 14,0-23,6)
- Prevention of invasive recurrence by radiotherapy does not diminish mortality at 10 years

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Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

Treatment	Cases, No	10-Year BCS Mortality (95%CI), %	Univariate HR (95% CI)	P Value	Multivariate ³ HR (95%)	P Value
Lumpectomy						
Without radiotherapy	19762	0.9 (0.7 - 1.1)	1 [Reference]		1 [Reference]	
With radiotherapy	42250	0.8 (0.7 – 1.0)	0.86 (0.67 – 1.10)	0.22	0.81 (0.63 – 1.04)	0.10
all	63319	0.8 (0.7 – 1.0)	1 [Reference]		1 [Reference]	
Unilateral mastectomy	19515	1.3 (1.1 – 1.5)	1.45 (1.18 – 1.79)	< 0.001	1.20 (0.96 – 1.50)	0.11

³ adjusted for year of diagnosis, age of diagnosis, ethnicity, income, ER-status, tumor size and grade

ORIGINAL ARTICLE – BREAST ONCOLOGY

Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years

Preeti Subhedar, MD¹, Cristina Olcese, BS¹, Sujata Patil, PhD², Monica Morrow, MD, FACS¹,
and Kimberly J. Van Zee, MS, MD, FACS¹

Breast Conserving Surgery Alone

Recurrence rate (95 % confidence interval)

Time period	5 year	10 year	HR	P value
1978-1998	19.1 % (15.6 - 23.2 %)	26% (22.0 - 30.7%)	1.0	----
1999-2010	8.9 % (7.1 - 11.3 %)	19% (14.9 – 23.1%)	0.59	0.0002

Breast Conserving Surgery and Radiotherapy

Recurrence rate (95 % confidence interval)

Time period	5 year	10 year	HR	P value
1978-1998	6.4% (4.1- 9.8 %)	13% (9.3 - 17.1 %)	1.0	----
1999-2010	4.9% (3.7 – 6.5 %)	11% (8.7- 14.2 %)	0.84	0.04



General Therapeutic Principles

Surgical excision (BCT, Mastectomy) is the therapeutic basis for the treatment of DCIS.

Adjuvant treatment (radiotherapy, hormonal treatment) must be discussed with the patient individually. Disadvantages must be balanced against risk reduction.

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Surgical Treatment for Histologically Proven DCIS I

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➤ 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		
➤	Histologically clear margins (R0)		2b	C	++
➤	Multifocal DCIS: BCT if feasible		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	+
	BCT		3b	B	-
	Mastectomy		3b	B	+
	In case of DCIS in the male breast		5	D	+
➤	ALND		2b	B	--

* Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.

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DCIS – Prognostic Factors for the Incidence of Local- / Locoregional Recurrence

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

Oxford / AGO LoE / GR

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

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Radiotherapy Statements

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- **Radiotherapy has no impact on survival** **LOE 1a**
- **Radiotherapy reduces the risk of local (invasive and non invasive) recurrences by 50 %** **LOE 1a**
- **Avoidance of invasive recurrence is probably not associated with survival benefit** **LOE 2b**
- **The absolute (individual) benefit of radiotherapy depends on the individual risk of local recurrence**
- **The number needed to treat (for any breast event) is 9 (over all risk groups)**

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DCIS Radiotherapy

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Radiotherapy after:

- Breast conserving surgery (BCS)
- Mastectomy

Modality:

- Partial breast radiotherapy (PBI)
- Hypofractionated radiotherapy regimens
- Radiotherapy boost on the tumor bed
 - Women younger than 45-50 years

1a A +*

2b B - -

3a D --

2b D -/+**

2b D --

2b C +/-

- * Side effects and disadvantages of radiotherapy must be balanced against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of “good risk” patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 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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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 - Statements

- **Postoperative antihormonal treatment has no impact on survival** **LOE 1a**
- **Postoperative antihormonal treatment may have a small effect on ipsilateral invasive recurrences** **LOE 1a**
- **Antihormonal treatment for DCIS has an effect on contralateral invasive cancer and ipsilateral and contralateral DCIS** **LOE 1a**
- **The number needed to treat for any breast event is 15** **LOE 1a**

Cochrane Analysis

Tamoxifen after DCIS (all/with Radiation)

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Guidelines Breast
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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.**

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Further
Information

References

DCIS Postoperative Systemic Treatment

**Oxford / AGO
LoE / GR**

- **Tamoxifen (only ER+)** **1a A +/-***
- **Aromatase inhibitor (only ER+) in
postmenopausal women only** **1b A +/-***
- **Trastuzumab (only Her2+)** **5 D --**

***Indication for treatment depends on risk factors, side effects
and patient preference**

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Local Recurrence of DCIS after Tumorectomy w/o Irradiation

**Oxford / AGO
LOE / GR**

After radiation

- **Simple mastectomy
+ SNB**
- **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	++
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Prognosis for invasive recurrences seems to be better than for primary invasive breast cancer. About 50% of recurrences are invasive.

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HEILEN**

Ductal Carcinoma in Situ (DCIS) ((2/17))

No further information

No references

Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/17)

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

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➤ **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*.
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- **Klinische Untersuchung**
- **Feinnadelpunktion / duktale Lavage**
- **Interdisziplinäre Tumorboard-Präsentation**

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ (4-5/17)

No further information

Reference:

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD; JAMA Oncol. doi:10.1001/jamaoncol.2015.2510 Published online August 20, 2015.

Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years (6/17)

No further information

Reference:

Preeti Subhedar, MD1, Cristina Olcese, BS1, Sujata Patil, PhD2, Monica Morrow, MD, FACS1, and Kimberly J. Van Zee, MS, MD, FACS1; Ann Surg Oncol (2015) 22:3273–3281

General Therapeutic Principles (7/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

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Surgical Treatment for Histologically Proven DCIS I (8/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung

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- **Intraoperative Schnellschnittdiagnostik**
- **Interdisziplinäre Tumorboard-Präsentation**

Surgical Treatment for Histologically Proven DCIS II (9/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung

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

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➤ **Mastektomie* (große Läsionen; keine sicheren Ränder im Nachresektat)**

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➤ **SNE***

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

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➤ **Axilladisektion**

DCIS – Prognostic Factors for the Incidence of Local- /Locoregional Recurrence (10/17)

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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➤ **Fokalität**

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- **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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Radiotherapy Statements (11/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

See next slides

DCIS Radiotherapy (12/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

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Radiotherapie nach:

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Sonderformen der Radiotherapie:

➤ Teilbrustbestrahlung

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➤ **Hypofraktionierte Radiotherapie**

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➤ **Boost-RT des Tumorbettes**

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Bei Patientinnen unter 45-50 Jahren

Cochrane Analysis – Radiation after Surgery (13/17)

No further information

No references

DCIS Postoperative Systemic Treatment - Statements (14/17)

No further information

References:

See next slides

Cochrane Analysis - Tamoxifen after DCIS (all/with radiation) (15/17)

No further information

Reference:

H. Staley, I. McCallum, J. Bruce. The Breast 23 (2014) 546e551

DCIS Postoperative Systemic Treatment (16/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung

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➤ Tamoxifen (nur ER+, nur BET)

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

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Mamounas, Norman Wolmark. Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. www.thelancet.com Published online December 10, 2015

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Local Recurrence of DCIS after Tumorectomy w/o Irradiation (17/17)

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
- **Sekundäre Tumorektomie führt zu Rezidiven in bis zu 30 % der Fälle (NSABP B17)**
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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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- **Versions 2002–2015:**
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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 ++

➤ **Minimal invasive biopsy***

1c A +

➤ **MRI****

1c B +/-

* If clinical examination, mammography, ultrasound and in some cases MRI are not able to determine the extension of lesion

** 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)

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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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

2a A ++

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

➤ 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 +/-

➤ Intraop. margin evaluation with margin probe

1b 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

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Axillary lymph node dissection (≥ 10 LN)

- To improve survival
- For staging
- For local control

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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	--
1a	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	+
-----------------	---	---

* Study participation recommended

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Surgical Treatment of Axillary Lymph Nodes post NACT (Neoadjuvant Chemotherapy) (N+)

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- **NACT (+/- Anti-HER 2 therapy) down-stages axillary nodes in 20->50%**
- **Possibility of avoiding ALND after NACT**
- **Reducing SLNB FNR by removal of >2sn and dual agent SN-mapping (radiocolloid + blue dye)**
- **Consideration of IHC staining in the SN**
- **Clip localization of positive nodes pre NACT**

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Axillary Intervention Before or After NACT

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SLNB before or after NACT in cN0						
SLNB before NACT				2b	B	+
SLNB after NACT				2b	B	+
Further surgical procedures depending on SLNB status						
cN-Status (before NST)	pN-Status (before NST)	cN-Status (after NST)		Surgical Procedure (after NST)		
cN0	pN0(sn)	-		nihil	1a	A
cN0	pN+(sn) (analog ACOSOG Z0011)	ycN0		nihil Re-SLNB alone ALND	3 2b 3	B B B
cN0	pN+(sn) (not analog ACOSOG Z0011)	ycN0		Re-SLNB alone ALND Axilla XRT	2b 2b 2b	B B B
cN0	not done	ycN0	ypN0 (sn)	SLNB alone ALND	2b 2b	B B
			ypN+ (sn)	ALND	2b	B
cN+	cN+ (CNB/FNA + clip placement)	ycN0		SLNB alone*	2b	B
		ycN+		ALND ALND	2b 2b	B B

* Analogue ACOSOGZ1071

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Sentinel Lymph Node Biopsy (SLNB): Indications I

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	1b	A	++
➤ Clinically (cN0) / sonographically neg. axilla			
➤ Add. FNA/CNB of LN (clinical/sonogr. suspicious + Clip localization if NACT) in order to enable SLNB	2a	B	+
➤ T 1-2	2b	A	++
➤ T 3, 4a-c	3b	B	+
➤ Multifocal / multicentric lesions	2b	B	+
➤ DCIS	3b	B	+
➤ Mastectomy	3b	B	+
➤ DCIS in male	5	D	+
➤ BCT	3b	B	-
➤ Male breast cancer	2b	B	+
➤ In the elderly	3b	B	+

Sentinel Lymph Node Excision (SNE): Indications II

Oxford / AGO LoE / GR

- | | | | |
|---|----|---|------|
| ➤ 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	+

**For „Surgery after neoadjuvant chemotherapy“ see 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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Breast Cancer Surgery Oncologic Aspects (2 and 3/16)

Further information and references:

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

Pretherapeutic assessment (4/16)

No further information

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Pre-operative staging (5/16)

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 (6/16)

No further information

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Breast conservation, surgical technical aspects (7/16)

No further information

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Breast Conservation Surgery (8/16)

No further information

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Axillary Lymph Node Dissection I (9/16)

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Surgical Treatment of Axillary Lymph Nodes Pre and Post Nact (10/16)

No further information

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Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies

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Axillary Intervention Before or After NACT (11/16)

No further information

No references

Sentinel Lymph Node Excision: Indications I (12/16)

No further information

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Sentinel Lymph Node Excision: Indications II (13/16)

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Sentinel Lymph node excision: Marking (14/16)

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Procedure after neoadjuvant treatment (15/16)

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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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.

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LoE / GR

- **Tumor adapted reduction
mammaplasty**
- **Local flap techniques**
- **Partial mastectomy
with tissue transfer**

2a B +

2a B +

3b B +/-

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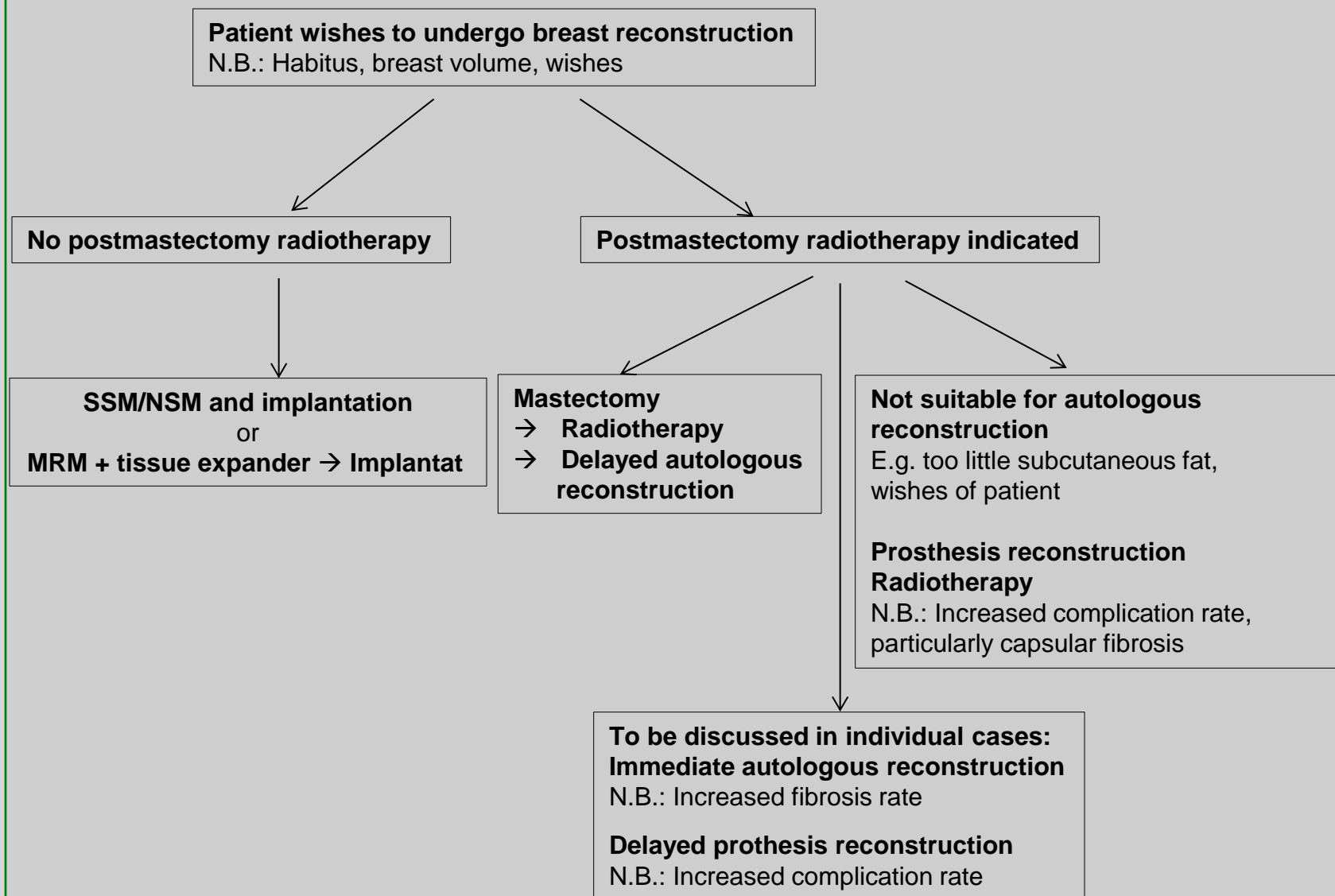
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Algorithm of Breast Reconstruction



Breast Reconstruction

General Considerations

AGO: ++

- **Counseling regarding all techniques, including techniques not offered at the own clinic, advantages and disadvantages**
- **Offer of a second opinion**
- **Consider neoadjuvant treatment in unfavourable tumor-breast-relation**
- **Consider adjustment surgery to achieve symmetry**
- **Prefer most convinient and aesthetically long lasting technique**
- **Caveat: delay in adjuvant treatment due to reconstruction**

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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

3b B ++

➤ Immediate BR

- Mandatory: SSM / NSM
- Avoidance of a postmastectomy syndrome
- No interference with adjuvant procedures (CHT, RT)

➤ Delayed BR

- Disadvantage: loss of skin envelope

3b B ++

➤ „Delayed-immediate“ BR

3b B +/-

Timing of Implant Based Reconstruction and Radiotherapy

Oxford / AGO LoE / GR

➤ Implant reconstruction (IR)

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

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

*MX = Mastektomie

Tissue Replacement Techniques and Meshes

**Oxford / AGO
LoE / GR**

- **Autologous tissue (e.g. autodermal graft, LDF*)**
- **Acellular dermal matrix (ADM)**
- **Synthetic mesh to fix the muscle**

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
LoE / GR**

Free tissue transfer

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

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

Advantage:

- DIEP and free TRAM, 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 and total failure rate
- Pre-reconstruction RT increases rate of vascular complications
- No higher patient satisfaction than with pedicled TRAM in multivariate analysis

Pedicled vs. Free Tissue Transfer

Oxford / AGO
LoE / GR

- **Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used**
- **Autologous abdominal-based reconstructions have the highest satisfaction in all patient groups without any difference**
- **Perforator flaps appear to have a higher risk for fat necrosis than free or pedicled TRAM**
- **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration in all flap techniques**

3a A ++

Flap-Implant Combination

Oxford / AGO
LoE / GR

LDF* + implant

- IR following RT
- IR prior to RT

Other flaps + implant

2b	C	+
3b	C	+
5	D	-
5	C	+/-

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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Guidelines Breast
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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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Further
Information

References

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Risk Reducing Bilateral Mastectomy in Healthy Women (RRBM)

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Guidelines Breast
Version 2016.1

- **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. bilateral 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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Further
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References

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*Counselling, risk prediction and follow-up in specialised centres recommended

Types of Risk Reducing (bilateral) Mastectomy (RRBM)

Oxford / AGO
LoE / GR

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Guidelines Breast
Version 2016.1

**Risk Reducing Mastectomy
reduces breast cancer incidence;
bc-spec mortality reduction likely**

➤ Simple mastectomy	2b	B	+
➤ RRBM by SSM*	2b	C	+
➤ RRBM by NSM* (NAC [#] sparing)	2b	C	+
➤ Contralateral prophylactic MX	4	C	+/-

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Information

References

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* SSM / NSM: Skin-/Nipple-Sparing Mastectomy

NAC: Nipple-Areola-Complex

Oncoplastic and Reconstructive Surgery (2/18):

Further information and references:

Screened data bases:

Pubmed 2006 - 2015, ASCO 2013 – 2015, SABCS 2013 – 2015, Cochrane data base (31.12.2015)

Screened guidelines: (download 13. Jan. 2016)

NCI (National Cancer Institute, 2015): <http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional>

ASCO (American Association of Clinical Oncology, Practice Guidelines, 2015)

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

CMA (Canadian Medical Association , 2015): <http://www.cmaj.ca/cgi/content/full/158/3/DC1>

NCCN (National Comprehensive Cancer Network , 2015):

http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Definition of oncoplastic surgery (3/18):

Further information:

AGO Voting for giving a new definition 45/0

References:

Definition modified after: Benjamin A; Kristine Calhoun: Oncoplastic techniques in breast conserving surgery.

<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 (4/18)

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AGO Voting for this slide and content 45/0

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Algorithm of Breast Reconstruction (5/18)

Further information:

AGO Voting for this slide and content 45/0

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Breast Reconstruction - General Considerations (6/18)

Further information:

Voting for this new slide and content 45/0

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Postmastectomy Reconstruction (7/18)

Further information:

Voting for this new slide and content 45/0

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Timing of Reconstruction (8/18)

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No voting this year

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Timing of Implant Based Reconstruction and Radiotherapy (9/18)

Further information:

AGO voting for implant reconstruction before radiation:

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Tissue replacement techniques and Meshes (10/18)

Further information:

Voting for new headline 45/0

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Lipotransfer (11/18)

Further information:

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 (12/18)

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Voting for whole content with one consent

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Free Tissue Transfer (13/18)

Further information:

Voting:

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

DIEP-flap + with one consent

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Pedicled vs. Free Tissue Transfer (14/18)

Further information:

No voting this year

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Flap-Implant Combination (15/18)

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No voting this year

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Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction (16/18)

Further information:

No voting this year

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Risk Reducing Bilateral Mastectomy in Healthy Women (RRBM) (17/18)

Further information:

No voting this year

Please see chapter breast Cancer Risk and Prevention

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Types of Risk Reducing Mastectomy (18/18)

Further information:

No voting this year

Please see chapter breast Cancer Risk and Prevention

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Adjuvant Endocrine Therapy

➤ Versions 2002–2015:

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

➤ Version 2016:

Jackisch / Schneeweiss

Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1

GR: A

AGO: ++

Endocrine responsiveness:

Immunohistochemistry (ER and / or PgR)

0% pos. cells:	endocrine non responsive
1-9% pos. cells:	endocrine low responsive
≥10% pos. cells:	endocrine responsive

Status unknown:

endocrine responsive

Adjuvant Endocrine Therapy

Assessment of Menopausal Status

Oxford / AGO
LoE / GR

Assessment of menopausal status

- Menstruation history +
- FSH, E2 ++

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

Oxford / AGO
LoE / GR

➤ **Endocrine responsive & doubtful:
Endocrine therapy**

1a A ++

➤ **Endocrine therapy
sequentially after CT**

2b C ++

➤ **Non-responsive:
No endocrine therapy**

1a A ++

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General Principles in Adjuvant Endocrine Therapy AGO ++

- **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

Oxford / AGO
LoE / GR

➤ **Tamoxifen* 5-10 yrs.**

1a A ++

➤ **GnRHa alone**

1a B +

(only if relevant contraindications for Tam)

**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 +/-

➤ **#OFS 5 yrs. + AI 5 yrs.**

1b B +/-

- * **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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Information

References

Premenopausal Patients

Adjuvant Endocrine Therapy

Oxford / AGO
LoE / GR

- | | | | |
|--|-----------|----------|------------|
| ➤ 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 | + |
| ➤ Reduction of POF* caused by adjuvant chemotherapy | 1b | B | +/- |

*POF: Premature ovarian failure

Postmenopausal Patients Adjuvant Endocrine Therapy

Oxford / AGO
LoE / GR

➤ **AI for 5 yrs.**

- Preference in lobular inv. cancers

1a A +
2b B ++

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

- Tam followed by AI (2-5 yrs.)*
- AI (2-5 yrs.)* followed by Tam
Preference in N+

1a A
1b C

➤ **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)

Oxford / AGO
LoE / GR

- Ovarian function protection

- CT + GnRHa
(GnRHa application > 2 weeks prior to chemotherapy)

1a B +/-

Impairment of CT – effect cannot be excluded!

- Fertility preservation counselling

4 C +

- Fertility preservation with
assisted reproduction therapy
(further information www.fertiprotect.de)

4 C +

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Testing Ovarian Reserve

Oxford / AGO
LoE / GR

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.

Contraceptive Options for Women after Diagnosis of Breast Cancer

Oxford / AGO
LoE / GR

- | | | | |
|---|-----------|----------|------------|
| ➤ Barrier methods | 5 | D | + |
| ➤ Sterilization (tubal ligation / vasectomy) | 5 | D | + |
| ➤ Non-hormonal intrauterine devices (IUDs) | 3b | D | + |
| ➤ Levonorgestrel-releasing IUDs | 2b | C | - |
| ➤ 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 | - |

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Emergency Contraception after Diagnosis of Breast Cancer

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➤ **Copper intrauterine devices (Cu-IUD)**

5 D +

➤ **Levonorgestrel, Ulipristal**

5 D +

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Ovarian Function Preservation – Comparison of Randomized Trials

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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 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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Autor	Jahr	Odds Ratio (95%CI)	Ereignisse GnRHa	Ereignisse Kontrolle
Gilani ^A	2007	0.06 (0.00, 1.24)	0/15	5/15
Badawy	2009	0.06 (0.02, 0.20)	4/39	26/39
Sverrisdottir_1	2009	0.19 (0.04, 1.06)	14/22	18/20
Sverrisdottir_2	2009	2.03 (0.31, 13.27)	27/29	20/23
Behringer [*]	2010	0.67 (0.08, 5.30)	7/10	7/9
Del Mastro	2011	0.25 (0.12, 0.52)	11/139	31/121
Gerber	2011	0.56 (0.19, 1.62)	9/30	13/30
Demeestere [*]	2012	1.14 (0.38, 3.42)	9/45	7/39
Munster	2012	1.24 (0.19, 8.20)	3/26	2/21
Elgindy_1	2013	0.75 (0.15, 3.79)	3/23	4/24
Elgindy_2	2013	0.63 (0.10, 4.21)	2/23	3/23
M-H Overall (I-squared = 55.8%, p = 0.012)		0.36 (0.25, 0.53)	89/401	136/364
Random Effect Pooled OR		0.43 (0.22, 0.84)		

Vorteil GnRHa / Vorteil Kontrolle

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TEXT /SOFT Joint Analysis

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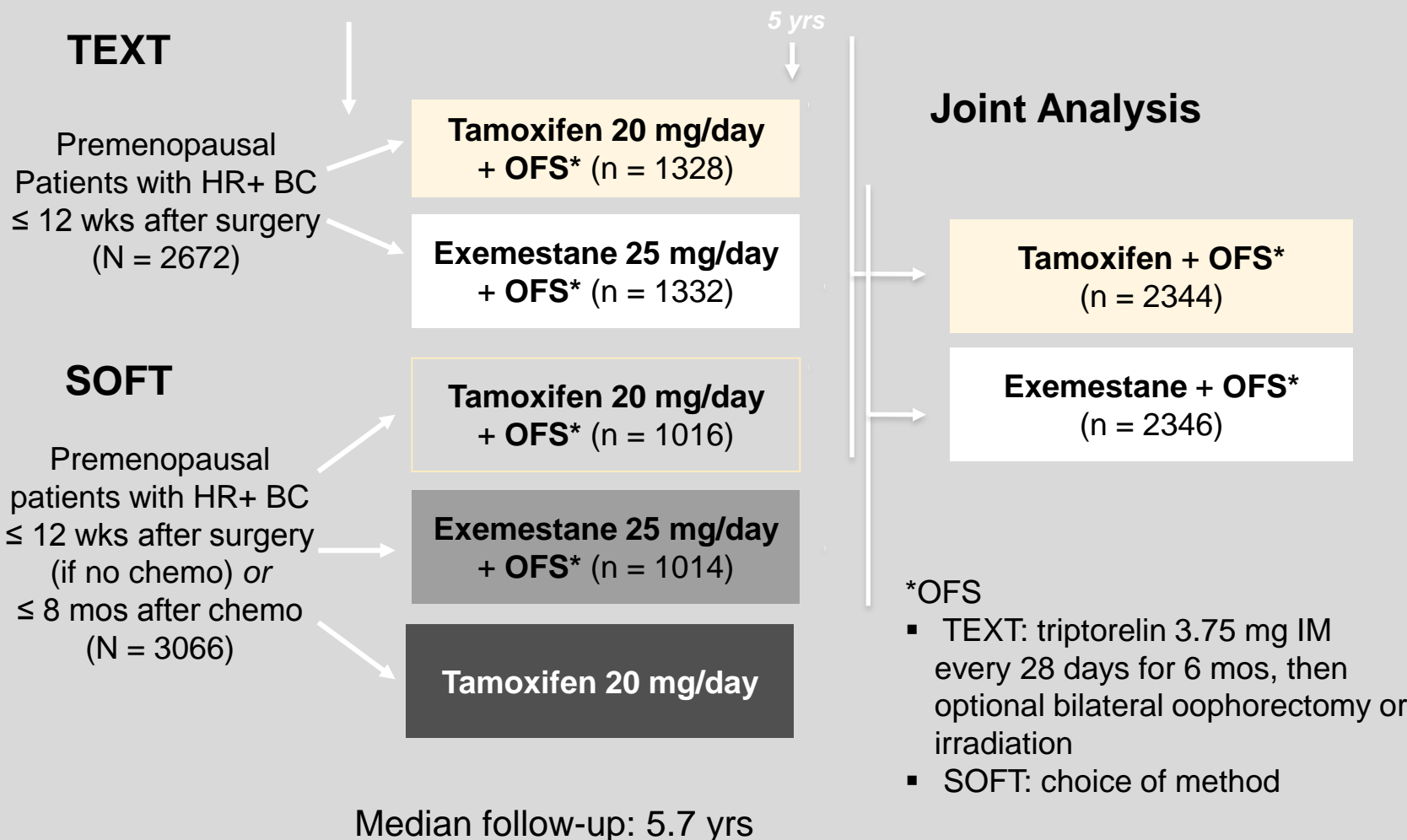
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Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Upfront and Extended Therapy

Trial	Source	AI	Indication	Pts	F/U mo	DFS/BCFS/TTR/TTDR/CBC	OS	Side Effects	Remarks
ATAC	ATAC Trialists' Group 2010	A	upfront vs T	6241	120	HR + patients: DFS HR 0.86, p=0.003 TTR 0.79, p=0.0002 TTDR 0.85, p=0.02	HR 0.87 p=0.4	SAE T>A gyn AE T>A VE T>A SE A>T	only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL → (Cella 2006)
BIG 1-98	BIG 1-98 Collaborative Group 2011	L	upfront ² vs T	4922	97	DFS = 0.86 P = 0,007	P = 0,048	SAE T=L gyn AE T>L TE T>L CE L>T SE L>T	L>T in particular in case of N+
NCIC CTG MA.27	Goss 2010	E	upfront vs A	7576	49	EFS HR 1,02 DDFS HR 0,95	ns	Osteoporosis A>E El. liver enzymes E>A Hyperlipidaemia A>E	Randomization for Celecoxib cancelled
Extended	Adjuvant		Therapy						
MA 17	Goss 2005	L	extended after 5y T vs P	5170	30	DFS HR 0.58, p<0.01 TTDR HR 0.60, p<0.01 CBC HR 0.63, p=0.13	HR 0,61 in N+, p=0,04	CE L=P SE L>P	QoL ↓ (Whelan 2005) Lipids → (Wasan 2005)
ABSCG6a	Jakesz 2007	A	extended after 5y T vs Nil	856	62	DFS HR 0.642 p=0.031	ns		
NSABP-B33	Mamounas 2008	E	Extended after 5y T Vs P	1598	30	DFS HR 0,68 p=0,07 RFS HR 0,44 p= 0,004	ns	SE E=P after 6 Mo	Grad 3 AE E>P 9%vs3%, p=0,03 Profit from E particular in N+

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

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Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Switching/Sequential trials

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

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

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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

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

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/21)

No further information

No references

Assessment of Steroid Hormone Receptor Status (3/21)

No further information

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Adjuvant Endocrine Therapy – Assessment of Menopausal Status (4/21)

No further information

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Adjuvant Endocrine Therapy (5/21)

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Adjuvant Endocrine Therapy (6/21)

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General Principles of Adjuvant Endocrine Therapy AGO ++ (7/21)

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Voting: 18/7

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Premenopausal Patients - Adjuvant endocrine therapy (8/21)

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.
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GnRHa alone 1a B + Voting: 100% acceptance

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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

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Premenopausal Patients – Adjuvant Endocrine Therapy (9/21)

Further information and references:

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

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

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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 (10/21)

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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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
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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
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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT) (11/21)

Further information and references:

Ovarian Function Protection

CT + GnRHα (Wechselwirkung mit CT unklar) 1b B +/-
(GnRHα 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.
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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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Testing ovarian reserve (12/21)

No further information

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Contraceptive Options for Women after Diagnosis of Breast Cancer (13/21)

No further information

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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.
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Emergency Contraception after Diagnosis of Breast Cancer(14/21)

No further information

No references

Ovarian Function Preservation - Comparison of Randomized Trials (15/21)

No further information

No references

Metaanalysis of GnRH for Prevention of Premature Ovarian Failure (16/21)

No further information

No references

TEXT/SOFT Joint Analysis (17/21)

No further information

No references

Aromataseinhibitors in Adjuvant Therapy (18/21)

No further information

No references

Aromataseinhibitors in Adjuvant Therapy – Overview over Published Trials (19/21)

No further information

No references

Assessment of Ovarian Reserve (20/21)

No further information

No references

10 Yrs versus 5 yrs Breast Cancer Mortality in ER+ (21/21)

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:**
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- **Versions 2003–2015:**
**Harbeck / Jackisch / Janni / Loibl / Lux /
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References

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**

++

+

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HER2+

- **Trastuzumab plus**
 - **Sequential A/T-based regimen with concurrent T + H**
 - **Anthracycline-free, carboplatinum-containing regimen**
 - **Anthracycline-free, taxane regimen for low tumor burden**
 - **Dose dense & escalated in case of high tumor burden**

++

++

+

+

+

TNBC

- **Conventionally dosed AT-based chemotherapy**
- **Dose dense & escalated**
- **Neoadjuvant platinum containing chemotherapy**

++

+

+

Adjuvant Chemotherapy without 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 ++

Further
Information

References

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Recommended Regimens for Adjuvant Chemotherapy

Oxford / AGO
LoE / GR

Anthracycline / taxane based regimen

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

Anthracycline-free regimen

➤ DC	D₇₅ C₆₀₀ x4	1b	B	+
➤ Pac mono	P₈₀ q1w x 12	1b	B	+/-
➤ CMF		1a	A	+/-

* Extrapolated from doxorubicin trials

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

Oxford / AGO
LoE / GR

Dose-dense regimen

➤ *EC q3w x 4 → Pac q1w x 12	1b	B	++
➤ AC q3w x 4 → Pac q1w x 12	1b	A	++
➤ AC q2w x 4 → Pac q2w x 4	1b	B	+
➤ EC q2w x 4 → Pac q2w x 4	1b	A	+
➤ EC q2w x 4 → Pac q1w x 12	1b	B	+

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

➤ E-Pac-C q2w	1b	A	++
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* Extrapolated from doxorubicin trials

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 | - - |

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Information

References

**FORSCHEN
LEHREN
HEILEN**

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 +/-

Further
Information

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
- Cardiac signs and symptoms

} }

3 monthly assessment of LVEF

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Further
Information

References

Adjuvant Treatment with Trastuzumab: Schedules

**Oxford / AGO
LoE / GR**

Simultaneously

- | | | | |
|---|-----------|----------|------------|
| ➤ With paclitaxel / docetaxel after AC / EC | 1b | A | ++ |
| ➤ With P q1w 12 x without A in pT < 3 cm, pN0 | 2b | B | + |
| ➤ With docetaxel and carboplatin | 1b | A | + |
| ➤ With anthracyclines | 2b | B | +/- |
| ➤ With taxanes dose-dense | 2b | B | + * |

Radiotherapy concurrent with Trastuzumab **2b** **B** **+**

*** Study participation recommended**

Adjuvant Therapy with Other Targeted Agents

Oxford / AGO
LoE / GR

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

1b^a B -

1b B -

- **Lapatinib + Trastuzumab**

1b^a B -

- **Pertuzumab**

5 D -

- **Bevacizumab**

1b B --

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Further
Information

References

FORSCHEN
LEHREN
HEILEN

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. Luisa Bonilla, Irit Ben-Aharon, Liat Vidal, Anat Gafter-Gvili, Leonard Leibovici, Salomon M. Stemmer. Dose-Dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials J Natl Cancer Inst 2010;102:1845–1854
3. 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.
4. 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, et al. Long-Term Follow-Up of the E1199 Phase III Trial Evaluating the Role of Taxane and Schedule in Operable Breast Cancer. J Clin Oncol 33:2353-60. 2015

Statement: Anthracycline/ taxane based regimen

AC → Pw A60C q3w x 4 → P80 qw1 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 (1b B ++)

Statement: Anthracycline/ taxane based regimen

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

Vote result of the AGO recommendation: 21 ++/ 13 + / 2 +/-

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..

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, Pippen 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, 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 32:2311-7.

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.* 26:675-82, 2014

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

Further information and references:

Statement: Dose-dense regimen

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

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

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 28:77-82, 2010.

Statement: Dose-dense regimen

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

Vote result of the AGO recommendation: 9 ++ / 15 +/- 1 +/- 0 - / 1 --

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;21:1431-9.

Statement: Dose-dense regimen

EC q3w / Pac q2w (1b 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;97:1724-33
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;100:305-10.

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. O'Shaughnessy J, Koeppen H, Xiao Y, et al. Patients with Slowly Proliferative Early Breast Cancer Have Low Five-Year Recurrence Rates in a Phase III Adjuvant Trial of Capecitabine. Clin Cancer Res. 2015, 21:4305-11
3. 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 (1b A - -)

Vote result of the AGO recommendation: 100%

1. Del Mastro L, De Placido S, Bruzzi P, et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. Lancet. 2015;385(9980):1863-72

Adjuvant treatment with trastuzumab I (8/12)

Further information and references:

Statements: Node-positive and node-negative disease (1a A ++)

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 (1a A ++ / 2b B + / 2b B +/-)

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 simultaneously with taxanes (1 A ++)

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 (1b A ++)

Vote result of the AGO recommendation: 100%

Duration Trastuzumab 2 year (1b A -)

Vote result of the AGO recommendation: 100%

Duration Trastuzumab 0.5 years (1b A +/-)

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. 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 – Cardia monitoring for CHF (10/12)

Further information and references:

Statement: Cardiac Monitoring (5 D ++)

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 (1b A ++)

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
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Statement: P q1w12 without A in pT < 3 cm pN0 (2b B +)

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. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015 Jan 8;372(2):134-41.

Statement: with docetaxel and carboplatin (1b A +)

Vote result of the AGO recommendation: 100%

1. Valero V, Forbes J, Pegram MD, Pienkowski T, Eiermann W, von Minckwitz G, Roche H, Martin M, Crown J, Mackey JR, Fumoleau P, Rolski J, Mrcic-Krmpotic Z, Jagiello-Grusfeld A, Riva A, Buyse M, Taupin H, Sauter G, Press MF, Slamon DJ. 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. *J Clin Oncol*. 2011 Jan 10;29(2):149-56.
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 (2b B+/-)

Vote result of the AGO recommendation: 100%

See references slide 8.

Statement: with taxanes dose-dense (2b B+)

Vote result of the AGO recommendation: 100%

See references slide 8.

Statement: radiotherapy concurrent with trastuzumab (2b B +)

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 *J Clin Oncol*. 2009 27(16):2638-44

Adjuvant Therapy with Other Agents (12/12)

Further information and references:

Statement: with Lapatinib (1b^a B -)
Delayed adjuvant treatment (1b B -)

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, Ejlersen 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. Edith A. Perez, Eileen Holmes, Evandro de Azambuja, Amylou Dueck, José Baselga, Giuseppe Viale, Jo Anne Zujewski, Aron Goldhirsch, Rocco Crescenzo, Kathleen I. Pritchard, Antonio C. Wolff, Christian Jackisch, Istvan Lang, Michael Untch, Ian Smith, Frances Boyle, Binghe Xu, Henry Gomez, Richard D. Gelber, Martine Piccart-Gebhart. Disease-free survival (DFS) in the lapatinib alone arm and expanded results of the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) in the adjuvant treatment of HER2-positive early breast cancer (EBC) ESMO 2014

Statement: with Lapatinib + Trastuzumab (1b^a B -)

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 (5 D -)

Vote result of the AGO recommendation: 100%

Trials are ongoing. No final results available.

Statement: Bevacizumab (1b B --)

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 2003–2015:**
**Bauerfeind / Blohmer / Dall / Fersis /
Friedrich / Göhring / Harbeck / Heinrich /
Huober / Jackisch / Kaufmann / Loibl /
Lux / von Minckwitz / Müller / Nitz /
Schneeweiss / Schütz / Solomayer /
Untch**
- **Version 2016:**
Liedtke / Untch

Subtype-specific General Systemic Strategies

AGO

If chemotherapy is indicated 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**
 - **Anthracycline-free, taxane regimen for low tumor burden**
 - **Dose dense & escalated in case of high tumor burden**

++

++

+

+

+

TNBC

- **Conventionally dosed AT-based chemotherapy**
- **Dose dense & escalated**
- **Neoadjuvant platinum containing chemotherapy**

++

+

+

Neoadjuvant Systemic Chemotherapy

Clinical Benefit

Oxford / AGO LoE / GR

- | | | | |
|---|----|---|------|
| ➤ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number) | 1a | A | |
| ➤ Pathological complete response is associated with improved survival in particular subgroups (HR+/HER2neg/Grade3, HER2-pos and TNBC) | 1b | A | |
| ➤ Can achieve operability in primary inoperable tumors | 1b | A | ++ |
| ➤ Improved options for breast conserving surgery | 1b | A | ++ |
| ➤ Allows individualization of therapy according to mid-course treatment effect | 1b | B | +* |
| ➤ Allows individualization of post-neoadjuvant treatment | 2b | B | +/-* |

* Study participation recommended

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 signatures	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumor infiltrating lymphocytes*	I	B	B	+
➤ PIK3CA mutation	II	B	B	+/-

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**defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (>50% lymphocytes of stromal area).*

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

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

**Oxford / AGO
LoE / GR**

- **AC or EC → D q3w or P q1w**

1a A ++

- **DAC**

2b A ++

- **Taxane followed by anthracycline**

2b B ++

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

1a A +

- **Platinum in TNBC (irrespective of BRCA status)**

1b B +*

- **Nab-Paclitaxel weekly instead of Paclitaxel weekly**

2b B +

- **In TNBC Nab-Paclitaxel qw instead of Paclitaxel qw**

1b B +/-

2b B +

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***Study participation recommended**

Potential Carboplatin Containing Regimens in the Neoadjuvant Setting

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Author	Study	Regimen	pCR rate	3-yr EFS rates
Sikov WM, et al. JCO 2015 SABCS 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)	TNBC ± Cb: 72% vs. 77% (HR 0.84 (95%CI 0.58- 1.22)
von Minckwitz G, et al. Lancet Oncol 2014 SABCS 2015	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)	TNBC ± Cb: 76% vs. 86% (HR 0.56 (95%CI 0.33- 0.96))
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 tumor region**

**Oxford / AGO
LoE / GR**

2b	B	++
2b	B	++
2b	B	++
2b	B	+
2b	B	+/-
5	D	++

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*** Study participation recommended**

Neoadjuvant Targeted Therapy in HER2 Positive Tumors

Oxford / AGO LoE / GR

- **Trastuzumab in combination with chemotherapy**
- **Lapatinib in combination with chemotherapy**
- **Lapatinib + Trastuzumab in combination with chemotherapy**
- **Pertuzumab + Trastuzumab in combination with chemotherapy**
- **Two anti-HER2 agents without chemotherapy**

1b A ++

1a B -

1a B +/-

2b B +

2b B +/-

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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 | +/- |

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Neoadjuvant Systemic Therapy Procedures in Case of Early Response

**Oxford / AGO
LoE / GR**

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

- **Complete all chemotherapy before
surgery i.e. ≥ 18 weeks of treatment**
- **In case of response after 2 cycles of
DAC in HR positive breast cancer
consider 8 instead of 6 cycles of DAC**

1b A ++

2b C +

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 surgery or radiotherapy**
- **Additional adjuvant chemotherapy with non cross-resistant regimen**

4 D ++*

4 D +/-*

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 according to
imaging result | 3b | C | + |

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Axillary Intervention Before or After NACT

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SLNB before or after NACT in cN0							
SLNB before NACT					2b	B	+
SLNB after NACT					2b	B	+
Further surgical procedures depending on SLNB status							
cN-Status (before NST)	pN-Status (before NST)	cN-Status (after NST)		Surgical Procedure (after NST)			
cN0	pN0(sn)	-		nihil	1a	A	+
cN0	pN+(sn) (analog ACOSOG Z0011)	ycN0		nihil Re-SLNB alone ALND	3 2b 3	B B B	+/- - +/-
cN0	pN+(sn) (not analog ACOSOG Z0011)	ycN0		Re-SLNB alone ALND Axilla XRT	2b 2b 2b	B B B	- + +
cN0	not done	ycN0	ypN0 (sn)	SLNB alone ALND	2b 2b	B B	+/- +/-
			ypN+ (sn)	ALND	2b	B	+
cN+	cN+ (CNB/FNA + clip placement)	ycN0 ycN+		SLNB alone* ALND ALND	2b 2b 2b	B B B	+/- + ++

* Analog ACOSOG Z1071

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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 within 2–3 weeks after surgery BCS

2b B ++

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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**
- **Complete pertuzumab treatment for 1 year in HER2-positive disease**
- **If insufficient response in case of non-pCR (invasive residual tumor in the breast and / or axillary nodes) after adequate NACT (anthracyclines, taxanes, 18 weeks)**
 - **Capecitabine adjuvant**
 - **Further chemotherapy**
 - **Experimental therapies in clinical trials**

1a A ++

2b B ++

3 C -

1b^a B +/-

3 C -

5 D +

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

➤ Postmenopausal patients:

- Who are inoperable
and can / will not receive chemotherapy
- Optimizes the option for breast conserving therapy
- Aromatase inhibitors (for > 3 months)
- Aromatase inhibitor + lapatinib (HER2+ BC)

Oxford / AGO
LoE / GR

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

➤ Premenopausal patients

- Who are inoperable
and can / will not receive chemotherapy
- Tamoxifen
- Aromatase inhibitors + LHRH

5	C	+
2b	C	+
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 1999-2016

ASCO 1999-2016

SABCS 1999-2016

ECCO/ESMO 1999-2016

Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information and references:

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)

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 (HR+/HER2neg/Grade3, HER2-pos and TNBC)

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 treatment

Abstimmungsergebnis der AGO-Empfehlungen: 2/7/20/1/0 (2016)

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, JCOm 32:
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: 0/15/10/0/0 (2016)

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
4. Denkert C, et al . Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2–Positive and Triple-Negative Primary Breast Cancers. JCO; 32: 2014

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

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, 2x2 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 \pm 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 (irrespective of BRCA status)

Abstimmungsergebnis der AGO-Empfehlungen: 3/18/8/0/0 (2016)

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
6. Byrski T, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. *Breast Cancer Res Treat* 2014; 147; 401
7. Von Minckwitz et al. ASCO 2014 (abs 1005)
8. Von Minckwitz G, et al "Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto)" SABCS 2015; Abstract S2-04.
9. Sikov WM, Berry DA, Perou CM, 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*, 2014

Nab-Paclitaxel weekly instead of Paclitaxel weekly

Abstimmungsergebnis der AGO-Empfehlungen: 0/4/5/0/0 (2016)

1. M Untch et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto—GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016, Published Online, February 8, 2016. [http://dx.doi.org/10.1016/S1470-2045\(15\)00542-2](http://dx.doi.org/10.1016/S1470-2045(15)00542-2)

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): in print
4. Gianni L et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). J Clin Oncol 33, 2015 (suppl; abstr 505)

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
2. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07

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 according to imaging result

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
3. Classe JM, Bordes V, Campion L, Mignotte H, Dravet F, Leveque J, Sagan C, Dupre PF, Body G, Giard S. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion. J Clin Oncol. 2009 Feb 10;27(5):726-32

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 in case of pCR

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

Complete pertuzumab treatment for 1 year in HER2-positive disease

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

If insufficient response in case of non pcr (invasive residual tumor in the breast and / or axillary nodes) after adequate nact (anthracyclines, taxanes, 18 weeks)

Capecitabine adjuvant

Abstimmungsergebnis der AGO-Empfehlungen: 0/2/27/4/0 (2016)

1. Lee S-J et al. A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X/JBCRG-04). San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract: S1-07

Further chemotherapy

Experimental therapies in clinical trials

Otherwise 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

START

Adjuvant Radiotherapy (RT)

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➤ Versions 2002–2015:

**Blohmer / Budach / Friedrichs / Göhring /
Janni / Kühn / Möbus / Scharl /
Seegenschmiedt / Souchon / Thomssen /
Untch / Wenz**

➤ Version 2016:

Thomssen / Budach / Wenz

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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**

Guidelines and Opinions

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St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:

Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractionated regimens involving 15 or 16 fractions are now widely accepted as standard of care.**

St. Gallen 2015: Gnant M, Breast Care 2015;10:124:

With respect to **hypofractionated** breast irradiation after breast conserving surgery, the panel felt that this is **appropriate for patients aged 50+** without chemotherapy or axillary involvement (89% Yes, 2% No, 9% Abstain), but **also for patients younger than 50 years** (71% Yes, 2% No, 27% Abstain), with uncertainty about patients with prior chemotherapy or axillary lymph node involvement (51% Yes, 18% No, 31% Abstain).

Statement J Harris, Dana Farber, Boston, SABCS 2015, PL1-01:

With regard to **hypofractionated whole breast irradiation**, cosmetic results are clearly better, patient satisfaction is improved, uncertainty about use in nodal RT. **We are using it just in about all (266 cGy x 15 with boost in about ½).**

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

LoE 1b B

AGO ++

< 50 years	Hypofractionated RT with sequential boost or conventional RT with integrated or sequential boost
≥ 50 years	Low risk*: hypofractionated RT without boost (15-16 fractions) High risk: RT as for <50 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)

***acc. definition for boost irradiation**

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 for BCT in Elderly Patient with 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	A	+/-

**Increase in local recurrence,
no influence on OS, decrease in toxicity,
salvage surgery and RT as an option in case of recurrence**

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

¹different 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

@10 yrs (95% C.I.)	Tamoxifen	Tamoxifen plus Radiotherapy	Hazard Ratio
Local recurrence free ($\Delta=8\%$)	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; n.s.)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR=1.20 (95% CI, 0.63 to 2.32; n.s.)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR=0.95 (95% CI, 0.77 to 1.18; n.s.)

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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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➤ Boost-RT (improves local control, no survival benefit)

➤ < 40 years

1b B ++

➤ 40-60 years

1b B +

➤ > 60 years, if G3 or >pT1

2b B +/-

➤ Intraoperative irradiation (intraop APBI)

➤ As boost-irradiation followed by WBI

2a B +

➤ As sole radiotherapy modality (IORT 50 kV, IOERT)**

➤ >50 yrs**

1b B +/-*

➤ >70 yrs**

1b B +

➤ Postoperative partial breast irradiation as sole radiotherapy modality (APBI)

➤ Interstitial brachytherapy

1b B +/-*

➤ >70 yrs**

1b B +

➤ Intracavity balloon technique

2b B -*

➤ IMRT***

2b B -*

* Study participation recommended; **only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery; ***no long term data

EORTC 22881-10882: Boost vs no Boost (Endpoint: ipsilateral breast recurrence)

@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 Tumor 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)

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

EORTC 22881-10882: Boost vs no Boost

(Endpoint: any first recurrence)

@15 yrs/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 Any First Recurrence				
All patients (Δ≥4%)	@15y	28.1%	32.1%	HR=0.92 (0.81-1.04), n.s.
	@20y	32,8%	38.7%	
≤40 years (Δ>6%)	@15y	41.5%	48.1%	HR=0.80 (0.56-1.15) , n.s.
	@20y	49.5%	56.8%	
41–50 years	@15y	34.0%	35.6%	HR=0.91 (0.71-1.16), n.s.
	@20y	38.6%	44.2%	
51–60 years	@15y	28.5%	28.7%	HR=0.96 (0.76-1.21), n.s.
	@20y	34.7%	36.2%	
>60 years	@15y	27.4%	29.1%	HR=0.94 (0.74-1.19), n.s.
	@20y	32.1%	32.8%	

(Median F/U 17.2 y) acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.

Postmastectomy Radiotherapy (PMRT)** to the Chest Wall

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- > 3 tumor infiltrated lymph nodes (Lnn.)
- 1–3 tumor infiltrated Lnn. high risk **AGO¹**
- 1–3 tumor infiltrated Lnn. low risk* **AGO¹**
- 1–3 tumor infiltrated Lnn. (every risk) **DEGRO¹**
- T3 / T4
 - pT3 pN0 R0 (and no additional risk factors)
 - If R0 is impossible to reach (for invasive tumor)
 - In young pts with high risk features
 - After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)
 - Omission of RT if ypT0 ypN0 after 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	+/-

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 Interventions in Patients with Positive Sentinel Lymph Nodes

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

- | | | | |
|---|----|---|------|
| ➤ if BCT and ACOSOG Z011-criteria fulfilled | 1b | B | +/-* |
| ➤ No axillary treatment | 1b | B | +/- |
| ➤ if mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled | 5 | D | +/-* |
| ➤ No further axillary treatment | 5 | D | +/- |
| ➤ if BCT and ACOSOG Z011-criteria <u>not</u> met | 1b | B | ++* |
| ➤ if mastectomy: PMRT and ACOSOG Z0011-criteria not met, or PMRT <u>not</u> planned | 1b | B | ++ |

>=3 pos. SLN:

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

*Study participation recommended

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)

RT to supra-/infraclavicular lymphatic regions

Oxford /AGO
LoE / GR

➤ **≥pN2a or Level III involved**

1b A ++

➤ **pN1a high risk***

2a B +

*tumor central or medial and
(G2-3 or ER/PgR-negative)

*tumor lateral and premenopausal and
(G2-3 or ER/PgR-negative)

➤ **pN0 high risk** with central or medial tumors**
** premenopausal and G2-3 and ER/PgR-negative

2a B +/-

➤ **After NACT/NAT (indications as for PMRT)**

AGO¹ 2b B +/-

➤ **After NACT/NAT if cN+ (indications acc. PMRT)**

DEGRO¹ 2b A +

¹ different interpretation of published data by AGO and DEGRO

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

Internal mammaria lymph node region (IMN)

- **pN0 high risk*** with central or medial tumor**
***premenopausal and G2-3 and ER/PgR-negative

Oxford /AGO
LoE / GR

1b B +/-

- **pN1a high risk***
*tumor central or medial, and
(G2-3 or ER/PgR-negative)
*tumor lateral and premenopausal and
(G2-3 or ER/PgR-negative)

2a B +

- **pN2a high risk****
**G2-3 or ER/PgR-negative

2a B +

- **pN1b-c, pN2c, pN3b**

2a B +

- **IMC-RT, if cardiac risk factors are present
or if trastuzumab is given**

2b A --

- **After NACT/NAT (indications as for PMRT) AGO¹**

2b B +/-

- **After NACT/NAT if cN+ (ind. acc. PMRT) DEGRO¹**

2b A +

¹ different interpretation of published data by AGO and DEGRO

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

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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**

Interaction between smoking and risk of irradiation-induced side effects

Oxford / AGO
LoE / GR

➤ **Enhanced risk of lung cancer secondary to breast cancer radiotherapy in smokers**

1a A

➤ **Inform patients about the risk**

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➤ **Recommend to stop smoking**

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References

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LEHREN
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Adjuvant Radiotherapy – (2/19)

Further information:

Search Strategy

Search Terms: Radiotherapy Breast Cancer

Source: Pubmed 1/2010 – 1/2016

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 (3/19)

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.

Adjuvant Radiotherapy - Slide 4/19

No further information

References:

1. Coates AS¹, Winer EP², Goldhirsch A³, Gelber RD⁴, Gnant M⁵, Piccart-Gebhart M⁶, Thürlimann B⁷, Senn HJ⁸; Panel Members. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
2. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A Brief Summary of the Consensus Discussion. Breast Care (Basel). 2015 Apr;10(2):124-30.
3. Harris JR. Critical Decision-Making in Radiation Therapy for Breast Cancer. Presentation at the San Antonio Breast Cancer Symposium 2016. PL1-01

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Whole Breast Irradiation (5/19) (Hypofractionation)

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.

Update 2016:

According the St. Gallen-Consensus, hypofractionated breast irradiation after breast conserving surgery involving 15 or 16 fractions are now widely accepted as standard of care (Coates A, AnnOncol 2015;26:1533:). The panel felt that this is appropriate for patients aged 50+ without chemotherapy or axillary involvement, but also for patients younger than 50 years, with uncertainty about patients with prior chemotherapy or axillary lymph node involvement.

At the San Antonio Breast Cancer Symposium 2015, JR Harris, Harvard Medical School, Boston, stated with regard to hypofractionated whole breast irradiation, that cosmetic results are clearly better, and patient satisfaction is improved; he added that some uncertainty exists about use in nodal RT. However in conclusion he reported that in his department they are using it just in about all (266 cGy x 15 with boost in about 1/2). (Harris JR SABCS 2015)

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.
5. Shaitelman SF¹, Khan AJ, Woodward WA, Arthur DW, Cuttino LW, Bloom ES, Shah C, Freedman GM, Wilkinson JB, Babiera GV, Julian TB, Vicini FA. Shortened radiation therapy schedules for early-stage breast cancer: a review of hypofractionated whole-breast irradiation and accelerated partial breast irradiation. *Breast J.* 2014 Mar-Apr;20(2):131-46.
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.
9. Budach W, Bölke E, Matuschek C. Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials. *Breast Care (Basel).* 2015 Aug;10(4):240-5.
10. Dellas K, Vonthein R, Zimmer J, Dinges S, Boicev AD, Andreas P, Fischer D, Winkler C, Ziegler A, Dunst J; ARO Study Group. Hypofractionation with simultaneous integrated boost for early breast cancer: results of the German multicenter phase II trial (ARO-2010-01). *Strahlenther Onkol.* 2014 Jul;190(7):646-53.

11. Coates AS1, Winer EP2, Goldhirsch A3, Gelber RD4, Gnant M5, Piccart-Gebhart M6, Thürlimann B7, Senn HJ8; Panel Members. Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol.* 2015 Aug;26(8):1533-46.
12. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A Brief Summary of the Consensus Discussion. *Breast Care (Basel).* 2015 Apr;10(2):124-30.
13. Harris JR. Critical Decision-Making in Radiation Therapy for Breast Cancer. Presentation at the San Antonio Breast Cancer Symposium 2016. PL1-01

Additional Information with Regard to Effects of Breast Radiotherapy (BCT) (6/19)

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.

2. 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.
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 (7/19)

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.
2. 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.
3. Hughes KS, Schnaper LA. Can older women with early breast cancer avoid radiation? The Lancet Oncology, Available online 28 January 2015

BCS >=70y <4 cm cN0: Tamoxifen vs. Tamoxifen + RT (8/19)

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, 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.

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation (9/19)

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. Young age and high-grade invasive ductal cancer were the most important risk factors for local relapse, in these patients the boost irradiation of 16 Gy significantly reduced the risk of relapse.

The first author of the EORTC Boost vs No Boost trial, H Bartelink, states in the conclusion of the publication: The extra radiation dose can be avoided in most patients older than age 60 years.

Reference:

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. Including Supplementary appendix
2. Jones HA, Antonini N, Hart AA, Peterse JL, Horiot JC, Collin F, Poortmans PM, Oei SB, Collette L, Struikmans H, Van den Bogaert WF, Fourquet A, Jager JJ, Schinagl DA, Wárlám-Rodenhuis CC, Bartelink H. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol.* 2009 Oct 20;27(30):4939-47.

References to the statements:

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, 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. Including Supplementary appendix.
2. Livi L, Borghesi S, Saieva C, Fambrini M, Iannalfi A, Greto D, Paiar F, Scoccianti S, Simontacchi G, Bianchi S, Cataliotti L, Biti G. Benefit of radiation boost after whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009 Nov 15;75(4):1029-34.

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

1. Antonini et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. 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.
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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. 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. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010 Jul 10;376(9735):91-102.

2. 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. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
3. 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. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol*. 2013 Dec;14(13):1269-77.

>70 yrs LoE 1b B AGO+/-

1. Abbott AM¹, Dossett LA¹, Loftus L¹, Sun W¹, Fulp W², Sokol GH³, Laronga C⁴. Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. *Am J Surg*. 2015 Oct;210(4):624-8.
2. 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. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.
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Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)

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.
2. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fishedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet*. 2016 Jan 16;387(10015):229-38.

Interstitial brachytherapy >70 yrs (LoE 1b B, AGO+)

1. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fishedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet*. 2016 Jan 16;387(10015):229-38.

Intracavity balloon technique (LoE 1b B AGO-)

1. 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. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg*. 2007 Oct;194(4):456-62.

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. 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. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer*. 2015 Jan 17. pii: S0959-8049(15)00002-7.
3. Olivotto 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. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol*. 2013 Nov 10;31(32):4038-45.

Boost vs no Boost: EORTC 22881-10882 Trial (10-11/19)

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.

References:

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, Elkhuisen 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 (12/19)**

Further information and references:

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 based on retrospective analyses 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%).

Shen H et al. 2015: High risk of local recurrence (HR = multivariate hazard ratio)

- Younger age (<40 yrs): HR 3.77 (2.16, 6.56)
- HER2 positive: HR 2.28 (1.41, 5.63)
- Lymphovascular invasion: HR 5.96 (2.90, 12.26)

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 radiation therapy to chest wall, infraclavicular region, supraclavicular area, internal mammary node, and any part of the axilla bed at risk.”.

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
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8. Shen H, Zhao L, Wang L, Liu X, Liu X, Liu J, Niu F, Lv S, Niu Y. Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1-T2 tumor and 1-3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases. *Tumour Biol.* 2015 Dec 2. [Epub ahead of print]

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.
2. 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). DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer. *Strahlenther Onkol.* 2014 Aug;190(8):705-14.
3. 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.

4. 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.
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.
6. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg*. 2013 Sep 11;2013:212979.
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9. Shen H, Zhao L, Wang L, Liu X, Liu X, Liu J, Niu F, Lv S, Niu Y. Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1-T2 tumor and 1-3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases. *Tumour Biol*. 2015 Dec 2. [Epub ahead of print]

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.
2. 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). DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer. *Strahlenther Onkol*. 2014 Aug;190(8):705-14.

3. 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.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. *ISRN Surg*. 2013 Sep 11;2013:212979.
5. 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.
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[“http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf”](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf) download 2016

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.
2. Valli MC; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Controversies in loco-regional treatment: post-mastectomy radiation for pT2-pT3N0 breast cancer arguments in favour. *Crit Rev Oncol Hematol*. 2012 Dec;84 Suppl 1:e70-4.

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.

2. Boutrus R, Taghian AG; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Post mastectomy radiation for large node negative breast cancer: time for a second look. Crit Rev Oncol Hematol. 2012 Dec;84 Suppl 1:e75-8.
3. Valli MC; Association of Radiotherapy and Oncology of the Mediterranean arEa (AROME). Controversies in loco-regional treatment: post-mastectomy radiation for pT2-pT3N0 breast cancer arguments in favour. Crit Rev Oncol Hematol. 2012 Dec;84 Suppl 1:e70-4.

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.
2. Freedman GM, Fowble BL, Hanlon AL, Myint MA, Hoffman JP, Sigurdson ER, Eisenberg BL, Goldstein LJ, Fein DA. A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. Int J Radiat Oncol Biol Phys. 1998 Jun 1;41(3):599-605.
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.
4. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
5. Rowell NP. Are mastectomy resection margins of clinical relevance? A systematic review. Breast. 2010 Feb;19(1):14-22.
6. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol. 2009 Apr;91(1):23-32.

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.
2. Cardoso F, Loibl S, Pagani O, et al.; European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer* 2012;48:3355-77.
3. Dragun AE, Huang B, Gupta S, Crew JB, Tucker TC. One decade later: trends and disparities in the application of post-mastectomy radiotherapy since the release of the American Society of Clinical Oncology clinical practice guidelines. *Int J Radiat Oncol Biol Phys* 2012;83:e591-6.
4. Mallon PT, McIntosh SA. Post mastectomy radiotherapy in breast cancer: a survey of current United Kingdom practice. *J BUON* 2012;17:245-8.
5. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. *Breast Cancer Res Treat* 2011;127:207-15.

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.
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.

4. Rusthoven CG¹, Rabinovitch RA¹, Jones BL¹, Koshy M², Amini A¹, Yeh N¹, Jackson MW¹, Fisher CM¹. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

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.
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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.

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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.

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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.

Radiotherapy of the Axilla (13/19)

No further information

References:

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 (14/19)

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 neither axillary dissection nor RT of 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.
2. 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: 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 (SCG/ICG) (15/19)

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%).

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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-/infralavicular lymphatic regions

RT to Supra-/infralavicular 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.
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4. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):307-16.
5. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. Radiat Oncol. 2015 Dec 21;10(1):258.
6. Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, Collette L, Fourquet A, Maingon P, Valli M, De Winter K, Marnitz S, Barillot I, Scandolaro L, Vonk E, Rodenhuis C, Marsiglia H, Weidner N, van Tienhoven G, Glanzmann C, Kuten A, Arriagada R, Bartelink H, Van den Bogaert W; EORTC Radiation Oncology and Breast Cancer Groups. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. N Engl J Med. 2015 Jul 23;373(4):317-27.

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

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.
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3. 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.
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RT to Supra-/infraclavicular lymphatic regions if pN1a high risk (LoE 2b B; AGO+)

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.

2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol*. 2015 Dec 21;10(1):258.
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RT to Supra-/infraclavicular lymphatic regions if pN1a low risk (LoE 2b B; AGO+/-)

1. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med*. 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol*. 2015 Dec 21;10(1):258.
3. 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.

4. 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.
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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 TJ, Olivetto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, Vallis KA, White JR, Rousseau P, Fortin A, Pierce LJ, Manchul L, Chafe S, Nolan MC, Craighead P, Bowen J, McCready DR, Pritchard KI, Gelmon K, Murray Y, Chapman JA, Chen BE, Levine MN; MA.20 Study Investigators. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med.* 2015 Jul 23;373(4):307-16.
2. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol.* 2015 Dec 21;10(1):258.
3. Whelan TJ, 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.
4. 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.
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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.
4. Rusthoven CG¹, Rabinovitch RA¹, Jones BL¹, Koshy M², Amini A¹, Yeh N¹, Jackson MW¹, Fisher CM¹. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. *Ann Oncol*. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN) - Slide 16/19

No further information

References:

Internal mammaria lymph node region (IMN)

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

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.
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5. 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.

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RT to Internal mammaria lymph node region (IMN) if pN1-pN2 and HR positive in patients who had systemic chemotherapy LoE 1b^a B; AGO+

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.
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5. 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.
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Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes (17/19)

No further information

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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 (18/19)

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.
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Interaction radiotherapy and smoking – Slide 19/19

No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Therapy Side Effects

START

Therapy Side Effects

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- **Versions 2004–2015:**
**Albert / Bischoff / Brunnert / Costa / Dall /
Friedrich / Friedrichs / Gerber / Göhring /
Huober / Jackisch / Lisboa / Lück / Müller /
Nitz / Schmidt / Souchon / Stickeler /
Untch**
- **Version 2016:**
Lück / Bischoff

Toxicity Assessment

Acute Toxicity According to WHO¹ or NCI-CTC²

Grade

0 none
1 mild
2 moderate
3 severe
4 life threatening

Information required

organs involved
type of toxicity
time interval after treatment
effect on general health status
treatment required
recovery achieved

Long-Term Toxicity No general assessment scale

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

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

Cytotoxic Anti-Cancer Drugs

Acute Toxicity I

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	Haematol. Toxicity	Nausea/ Vomit.	Alopecia	Mucositis/ Stomatitis	Cardiac Toxicity	Renal Toxicity	Hepatic Toxicity
Cyclophosphamide	++	++	+	+	+	++	
Methotrexate	++	+	+	++	+	++	+
5-Fluorouracil	++	++		++	+		
Carboplatin	++	++	+			++	
Cisplatin	+	+++				+++	
Capecitabine	+	+		+			
Gemcitabine	++	+		+			+
Epi-/Doxorubicin	++	++	+++	++	+		
Pegliposomal Doxorubicin	+	+	+	++	(+)		
Liposomal Doxorubicin	+	+	+	++	(+)		
Mitoxantrone	++	++	+	+	+		
Paclitaxel	++	+	+++	+			+
nab-Paclitaxel	+	+	+++				+
Docetaxel	++	+	+++	++			
Vinorelbine	++		(+)	+			
Eribulin	++	+	+				

Cytotoxic Anti-Cancer Drugs

Acute Toxicity II

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	Allergy	Bladder	Neuro- toxicity	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

VOLUME 32 · NUMBER 18 · JUNE 20 2014

JOURNAL OF CLINICAL ONCOLOGY

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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

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- **Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)**
- **Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity**
- **Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:**
 - **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 %)**

**Oxford / AGO
LoE / GR**

2b B

1b B

2b B

3b C +

Feasibility of Treatment Combinations Considering Toxicities

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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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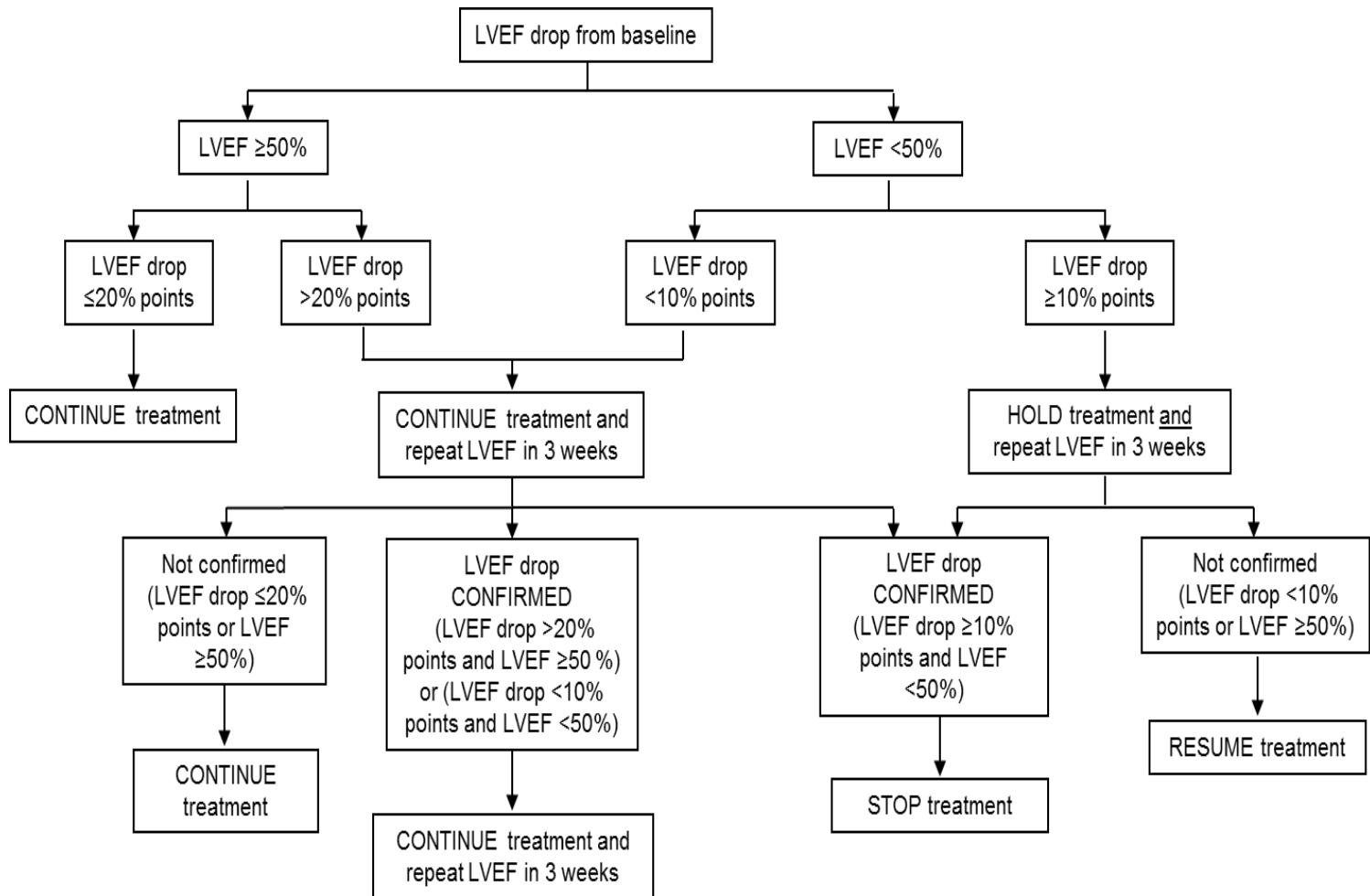
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Secondary Malignancies I

Oxford / LoE

- **With regard to solid tumors, chemotherapy induced secondary malignancies are rare events** 2a
- **Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0,2–0,4 % within 10 - 15 years** 2a
- **Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0,2–1,7 % within 8 to 10 years** 2a
- **PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5-1%** 2b
- **Radiotherapy increases the risk of leukaemia by 0,2–0,4% in patients treated with anthracycline-containing chemotherapy** 2b
- **Tamoxifen approximately doubles the risk for developing endometrial cancer** 2b

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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 +

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(Therapy Associated) Sleeping disturbance

Oxford / AGO
LoE / GR

- **Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)**

2a B

- **Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life**

1b A ++

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(Therapy Associated) Depression

Oxford /LoE

- Depression is an often reported adverse event in breast cancer patients (20–30%)

2a B

- Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients

1b A

- Antidepressants have shown to improve depression in breast cancer patients

1b A

- Regular exercise participation can prevent depression among breast cancer survivors

2b B +

(Therapy Associated) Cognitive Impairment

Oxford / AGO
LoE / GR

- **Therapy-related cognitive deficits
(chemobrain frequently described (16–75%))**
- **Cognitive-behavioral therapy is beneficial for
cognitive function**
- **Methylphenidate might improve cognitive
function in patients with cancer**

2a B

2b B

3a C

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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** **1b**
- **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%)** **1b**
- **Acute phase reaction (IV Amino-BPs, DB) 10–30%** **1b**
- **Gastrointestinal side effects (oral BPs) 2–10%** **2b**

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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

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Trastuzumab

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

Bevacizumab

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

Pertuzumab

- **Skin rash, diarrhea, mucositis**

T-DM1

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

Oxford / AGO
LoE / GR

1b A

2b B

1a A

2b B

2b B

Small Molecules

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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

Immun-Checkpoint Inhibitors

➤ Therapeutic options (Antibodies)

➤ PD1 /PD-L1

➤ Nivolumab

➤ Pembrolizumab

➤ Atezolizumab

➤ CTLA-4

➤ Ipilimumab

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Immun-Checkpoint Inhibitoren

➤ Side effects \geq Grad 3

- Diarrhoe
- Fatigue
- Colitis
- Hypophysitis
- Hepatitis
- Skin changes
- Thyreoiditis

Therapy Side Effects (2/24)

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 (3/24)

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 (4/24)

No further information

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2. Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ.: Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011 Sep;22(9):1939-47.
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4. Jim HS et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012 Oct 10;30(29):3578-87
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6. Kaufmann PA, Awada A, Twelves C et al. Phase 3 open label randomized multicenter study Eribulin Mesylate versus Capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclins and taxanes SABCS 2012, abstract S6-6

Cytotoxic Anti-Cancer Drugs – Acute Toxicity II (5/24)

No further information

References:
see slide 4

ASCO Guidelines PNP (6/24)

No further information

No references

Long-Term Toxicity Cardiotoxicity I (7/24)

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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Feasibility of Treatment Combinations Considering Toxicities (8/24)

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 (9/24)

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 (10/24)

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 (11/24)

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) (12/24)

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 (13/24)

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 (14/24)

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 (15/24)

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 (16/24)

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 (17/24)

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) (18/24)

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 (19/24)

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) (20/24)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 18-19/22!

Key-Toxicities Antibodies/Antibody-drug-conjugates – Small Molecules (21/24) and (22/24)

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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Pertuzumab

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2. Baselga J, Cortes J, Kim S-B et al. Pertuzumab plus Trastuzumab plus Docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366:109-119

T-DMI

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Everolimus:

1. Baselga J, Campone M, Rugo H et al. Everolimus in postmenopausal hormone receptor positive advanced breast cancer. *N Engl J Med* 2012;366: 520-529

Immun-Checkpoint Inhibitors (23-24/24)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Supportive Care

Supportive Care

➤ **Version 2002:**
Diel

➤ **Versions 2003–2015:**
**Bauerfeind / Bischoff / Costa / Dall / Diel /
Fersis / Hanf / Heinrich / Jackisch / von
Minckwitz / Möbus / Oberhoff / Rody /
Schaller / Scharl / Schmidt / Schütz**

➤ **Version 2016:**
Diel / Möbus

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>“**

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):

„Supportive Therapie bei onkologischen Patientinnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, final consensus Nov 2015, planned release: 31.5.2016

Further
Information

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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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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 A ++
- **Therapeutic usage for FNP**

1a A +/-
- **Start related to chemotherapy and duration**
 - **Pegfilgrastim day 2**

1b A ++
 - **Lipegfilgrastim day 2**

1b A ++
 - **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
- Thomas J. Smith, Kari Bohlke, Gary H. Lyman et al. Recommendations for the use of WBC Growth factors: American society of clinical practice guideline update. J Clin Oncol 2015;28:3199-3212
- Volovat C, Bondarenko IM, Gladkov OA et al. Phase III randomized double-blind placebo-controlled, multicentre study of lipegfilgrastim in patients with non-small lung cancers receiving myelosuppressive therapy. SpringerPlus 2015;4:316

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 $<500\text{ cells/mm}^3$ or expected to fall to $<500\text{ cells/mm}^3$)

**Oxford / AGO
LoE / GR**

➤ Clinical examination	5	D	++
➤ Daily evaluation	5	D	++
➤ Hospitalization of high risk patients	1b	A	++
➤ Homecare in low risk patients	1b	A	+
➤ Differential blood count	5	D	++
➤ Blood cultures	5	D	++
➤ Imaging of lungs	3	C	++
➤ Immediate initial empiric antibiotic therapy	1a	A	++
➤ Empiric antifungal therapy 4–7d			
in case of failure of antibiotic therapy	1b	A	++
➤ G-CSF for treatment (not prophylactic)	2b	B	+/-

Calculated Antibiotic Therapy in FN

Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO)
www.dgho-infektionen.de
regularly issues such recommendations in German.

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Dexrazoxane

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

**Oxford / AGO
LoE / GR**

➤ **Treatment of anthracycline extravasation**

2b B ++

➤ **In cardiac risk patients**

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

5 D ++

Paravasation Dexrazoxane

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs

Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

**Otherwise or if treatment with dexrazoxane is not indicated,
following measures are recommended**

- 1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling**
- 2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to dry on air. The interval may be extended to 6 hours from day 4 onward.**

Antiemetic Therapy

MASCC/ESMO antiemetic-guidelines

NCCN guidelines

Oxford / AGO
LoE / GR

- | | | | |
|---|----|---|----|
| ➤ 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 | ++ |
| ➤ Fixed antiemetic combination therapy | 1b | A | ++ |
| ➤ Metoclopramide | 3b | C | + |

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Supportive Therapy

Antiemetics

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Hesketh, Paul J, Bohlke K, Lyman GH et al. Antiemetics: American society of clinical oncology focused guideline update. J Clin Oncol 2016;34:381-6

Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy induced nausea and vomiting. Ann Oncol 2015;26:1081-90.

Hesketh PJ, Aapro M, Jordan K et al. A review of NEPA, a novel fixed antiemetic combination with the potential for enhancing guideline adherence and improving control of chemotherapy-induced nausea and vomiting. Biomed Res Int 2015;65:1879

Schwartzberg LS, Rugo HS, Aapro M. New and emerging therapeutic options for the management of chemotherapy-induced nausea and vomiting Clin Adv Hematol Oncol 2015;15(3 Suppl. 3):3-13

Jordan K, Schaffrath F, Jahn F et al. Neuropharmacology and management of chemotherapy-induced nausea and vomiting in patients with breast cancer. Breast Care 2014;9:246-53

Further
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References

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 Kombinations partner (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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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/ 23)

No further information

No references

Guideline spectrum (3/23)

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) (4/23)

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.

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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]
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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 (5/23)

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 (6/23)

No further information

References:

1. Rodgers GM und Giliath 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 (7/23)

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

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Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline. Christopher R. Flowers, Jerome Seidenfeld, Eric J. Bow, Clare Karten, Charise Gleason, Douglas K. Hawley, Nicole M. Kuderer, Amelia A. Langston, Kieren A. Marr, Kenneth V.I. Rolston, and Scott D. Ramsey
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013 The latest version is at
<http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.45.8661> published ahead of Print on January 14, 2013 as
10.1200/JCO.2012.45.8661

EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment (8/23)

No further information

No references

Relevant guidelines (9/23)

No further information

Reference:

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Mucositis (10/23)

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 (11/23)

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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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
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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 (12/23)

No further information

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Management of Febrile Neutropenia (13/23)

Further information:

The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines.

A Cochrane review sought to evaluate the safety and effectiveness of adding colony stimulating factors (CSF) to antibiotic therapy when treating febrile neutropenia caused by cancer chemotherapy. The authors looked for all randomized controlled trials (RCTs) that compare CSF plus antibiotics versus antibiotics alone for the treatment of established febrile neutropenia in adults and children. After inclusion of 13 studies the authors concluded, that „ the use of CSF in patients with febrile neutropenia due to cancer chemotherapy does not affect overall mortality, but reduces the amount of time spent in hospital and the neutrophil recovery period. It was not clear whether CSF has an effect on infection-related mortality.“

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NCCN:

NCCN Guidelines Version 1.2012 Panel Members Myeloid Growth Factors;
http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf

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

Calculated Antibiotic Therapy in FN (14/23)

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 (15/23)

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 (16/23)

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.

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Im Focus Onkologie 2010;6:50-55.

Antiemetic Therapy (17/23)

Further information:

Nausea and vomiting are two of the most severe problems for patients treated with chemotherapy. Until the late 1970s, nausea and vomiting induced by chemotherapy was an almost neglected research area. With the introduction of cisplatin, the cytotoxin with the highest emetic potential, research was stimulated and has now resulted in the development of two new classes of antiemetics, the serotonin and neurokinin antagonists. A large number of trials have fine-tuned antiemetic therapy and made evidence-based recommendations possible for the majority of patients receiving chemotherapy. A systematic Review summarizes recommendations from the evidence-based guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC).

The combination of ondansetron, dexamethasone and aprepitant is able to protect 66–78% of patients from emesis and 48–49% from nausea during the first cycle of cisplatin-based chemotherapy. In a subsequent trial, single-dose intravenous fosaprepitant (150 mg) given with ondansetron and dexamethasone was noninferior to standard 3-day oral aprepitant in preventing CINV during OP and DP.

In women receiving cyclophosphamide/anthracycline-based chemotherapy for breast cancer, the corresponding figures are 76% and 33%. In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to aprepitant but instead had similar efficacy and toxicity in preventing delayed emesis.

New antiemetics have been highly successful in the prophylaxis of emesis, but are less effective in the prevention of nausea. There is, therefore, a particular interest in initiating trials to investigate agents with potential anti-nausea effect, such as olanzapine. Guidelines such as the MASCC antiemetic guidelines are only useful if they are continuously updated and implemented in the daily clinic. To encourage implementation, the MASCC guidelines have been translated into several languages, are updated every 6 months (as new data arise), and are always accessible on the MASCC website.

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Relevant Guidelines

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

Antiemetische Prophylaxe gemäß MASCC- und ASCO-Guidelines

[PDF-Datei (auf www.krebsgesellschaft.de)]

Kurzgefasste interdisziplinäre Leitlinie 2008 der Deutschen Krebsgesellschaft, die unter der Verantwortung der ASO bzw. ASORS erstellt wurde.

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Supportive Therapie: Antiemetics (18-19/23)

No further information

No references

Analgesia (20/23)

No further information

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Relevant guidelines

Deutsche Gesellschaft zum Studium des Schmerzes, www.dgss.org

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

Diarrhea (21/23)

No further information

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Relevant Guidelines

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Constipation (22/23)

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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Palliative Care (23/23)

Further information

Growing evidence and increasing awareness in international recommendations underlines the relevance of combined standard oncology care and palliative care. This should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden. It is evident that the access to palliative care, including effective control of pain and other symptoms, is important in the treatment of metastatic breast cancer patients.

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Diagnosis And Treatment Of Patients With Primary And Metastatic Breast Cancer

Breast Cancer: Specific Situations

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➤ **Versions 2005-2015:**

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Göhring / Harbeck / Huober / Janni / Loibl /
Lück / Lux / Maass / Mundhenke / Oberhoff /
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- **Young patients**
- **Pregnancy-associated BC**
- **Elderly patients**
- **Male patients**
- **Inflammatory BC**
- **Occult Primary, CUP (Carcinoma of unknown primary)**
- **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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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)**
- **SLNE during 1st trimester**
 - **Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs**
 - **Blue dye (has not been tested in pregnant animals or humans)**

4	C	++
5	D	+/-
4	C	++
4	C	+
5	D	+/-
4	C	++
4	C	--

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* Participation in register study recommended

Breast Cancer During Pregnancy*

Oxford / AGO

LoE / GR

- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only
after first trimester
(indication as in non-pregnant)
 - Anthracyclines: AC, EC
 - Taxanes
 - MTX (e.g. CMF)
 - Endocrine treatment
- HER2-neu targeted treatment
- Bisphosphonates, denosumab

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

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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 ++**

Further
Information

References

Pregnancy Associated Breast Cancer*: Outcome

Oxford

LoE

- **BC during pregnancy / lactation**
 - Adequate treatment is essential

- **Pregnancy and lactation after BC**
 - Outcome not compromised

3a

3a

Geriatric Assessment

- **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**
 - **Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)**

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**
 - **Hypofractionation or sole IORT / IOERT**
 - **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	+
1b	A	+
1b	A	+/-
2b	C	+

AGO

DEGRO

*Study participation recommended

**Population > 70 y, hormone receptor positive and if endocrine therapy is planned (CAVE: increased risk local recurrence)

Different interpretation of published data by AGO and DEGRO

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 or
IORT / IOERT as sole radiotherapy modality | 1b | B | + |
| ➤ No chemotherapy if >70 years and negative
risk-benefit analysis | 2b | C | + |

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Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

Oxford / AGO LoE / GR

- | | | | |
|---|------------|----------|------------|
| ➤ Diagnostic work-up as in women | 4 | C | + |
| ➤ Mammography | 3b | C | +/- |
| ➤ Ultrasound | 2b | B | ++ |
| ➤ Standard-surgery: Mastectomy | 4 | C | ++* |
| ➤ BCT is an option (tumor breast relation) | 4 | C | +* |
| ➤ Sentinel-node excision (SNE) | 2b | B | + |
| ➤ Radiotherapy as in women
(consider tumor breast relation!) | 4 | C | + |
| ➤ Genetic counselling if <u>one</u> additional
relative affected (breast/ovarian cancer) | 2b | B | ++ |
| ➤ Genetic counselling without affected relatives | 2b | B | + |
| ➤ Screening for 2nd malignancies
according to guidelines | GCP | | ++ |

***Participation in register study recommended**

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**

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Inflammatory Breast Cancer (IBC, cT4d)

In case of invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d

**Oxford / AGO
LOE / GR**

➤ Survival benefit by trimodal treatment (NACT, MRM, RT)	2b	B	++
➤ Staging	2c	B	++
➤ Skin punch biopsy (at least 2; detection rate < 75%)	2c	B	+
➤ Preoperative chemotherapy	2c	B	++
➤ Regimens as in non-inflammatory BC: anthracycline and taxane-based	2b	B	++
➤ In HER2-pos. BC, addition of trastuzumab	2b	B	++
➤ In HER2-pos. BC, addition of trastuzumab & pertuzumab	2b	B	++
➤ In HER2-neg. addition of bevacizumab	2b	C	+/-
➤ Mastectomy after chemotherapy	2c	B	++
➤ Breast conserving therapy in case of pCR	2b	C	+/-
➤ Sentinel excision only	3b	C	--
➤ Radiotherapy (PMRT)	2c	B	++
➤ Postoperative systemic therapy as in non-inflammatory BC	4	C	++

Benefit from Trimodal Treatment in Inflammatory Breast Cancer

Median survival probability		
Trimodal therapy	72 months	p<0.05
Surgery alone	26 months	

Overall survival-probability (OS)	10 years-OS	5 years-OS
Trimodal therapy	55.4%	37.3%
Surgery & chemotherapy	42.9%	28.5%
Surgery & radiotherapy	40.7%	23.5%
Surgery alone		16.5%

Multivariate analysis of OS	Hazard Ratio	95% CI
Surgery & chemotherapy & RT (trimodal therapy)	1.00	-
Surgery & chemotherapy	1.64	1.46 to 1.84
Surgery & radiotherapy	1.47	0.96 to 2.24
Surgery alone	2.28	1.80 to 2.89

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 (AGO)	3b	B	+

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Paget' s Disease of the Breast

Oxford / AGO
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 -

Malignant and Borderline Phyllodes 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!)

Oxford / AGO
LOE / GR

Treatment of Primary Disease:

- **Mammography, sonography to determine extent of disease**
- **Preoperative MRI to determine the extent of disease**
- **Diagnosis by core biopsy**
- **Diagnosis by FNB**
- **Staging (CT thorax & abd.; angiosarcoma: MRI brain)**
- **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 if high risk (grade II-III, size > 5 cm, R1)**
- **Regional hyperthermia* (to improve local control and DFS in angiosarcoma) plus chemotherapy and/or radiotherapy**

3a	C	--
3a	C	++
3a	C	++
3a	C	--
4	D	++
3a	C	++
3a	C	++
3a	C	+/-
3a	C	-
3a	C	+/-
4	C	+/-

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

*Therapy in specialized centres recommended

Sarcoma / Angiosarcoma of the Breast

Treatment of local recurrence and metastases

Oxford / AGO
LOE / GR

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 (e.g. in angiosarcoma)
- Trabectedin (after anthracycline / ifosfamide failure in leiomyosarcoma)

4 C ++

2b B +

4 C +/-

2b B +

Breast Cancer: Specific Situations (2/20)

Further information:

Update January 2016 – Thomssen / Harbeck
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 – Jan 2016, ASCO 2005 – 2015, SABCS 2005 – 2015, ECCO/ESMO (2005 – 2015), EBCC (2005 – 2015),
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 (3/20)

No further information

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Breast Cancer in Young Women ≤ 35 years (4/20)

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.

International Guidelines:

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

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Surgery in young women (Surgery like ≥ 35 y - in particular BCT)

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Breast Cancer During Pregnancy or Breast Feeding (5/20)

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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Outcome information (e.g. GBG registry):

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Statement: Breast imaging & biopsy like in non-pregnant

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2. Ahn BY et al., Pregnancy and lactation-associated breast cancer: mammographic and sonographic findings. *J Ultrasound Med* 2003, 491-497
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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

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Statement: Surgery like in non-pregnant patients

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Statement: „Sentinel node biopsy“ during pregnancy

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2. Gentilini O et al., Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004, 15: 1348-1351
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Reviews

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Breast Cancer During Pregnancy (6/20)

No further information

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In general

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Statement: Radiotherapy during pregnancy

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

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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

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Statement: Taxanes

1. Mir O et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol.* 2008 Apr;19(4):607-13.
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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

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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)
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Statement Bisphosphonate during pregnancy

18. Levy S, Fayed 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.
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General information: Chemotherapy during pregnancy

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Breast cancer during pregnancy (7/20)

Further information:

These statements are derived from common sense and literature cannot fully be assigned.

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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.
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Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome

1. 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

1. 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

1. Williams Obstetrics lecture book
2. 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 (8/20)

Further information:

The outcome of pregnant breast cancer patients do not seem to be inferior to those being non pregnant. Data investigating this topic are inconsistent incorporating pregnant patients and PABC. A recent study however demonstrated a poorer survival for PABC. Most investigations did not report on the applied therapy which might be a confounding factor.

Pregnancy after breast cancer is safe and does not compromise the outcome. A healthy mother effect might be the reason, however, larger case series including also patients with advanced disease proposed additional effects.

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In general

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Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately

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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

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Geriatric Assessment (9/20)

Further information:

There is no accepted definition of the “older patient” but criteria exist for the assessment of biological age. The distinction between fit patients, vulnerable patients and frail patients has been established. Geriatric evaluation is an optimal tool for individually assessing the feasibility of treatment,

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Treatment for Fit Elderly Patients (10/20)

Further information:

Chemotherapy is feasible in fit elderly pts. The first randomized prospective trial in >600 pts. Demonstrated a survival benefit for patients treated with AC or CMF compared to those treated with Capecitabine alone. In an unplanned subset analysis, patients with hormone receptor negative disease derived the highest benefit from the combination therapy. Another German trial (ICE II) is investigating a combination of capecitabine with nab-paclitaxel compared to EC/CMF. In a retrospective analysis of four German randomized (neo)adjuvant trials taxanes seem feasible. Sequence therapies should be preferred; paclitaxel weekly seems to be the preferred taxane regimen in terms of toxicity for elderly pts. The study by Jones et al. evaluating TC as anthracycline free regimen showed especially good results in pts. older than 65 years.

In respect to older patients, current data increasingly suggest that the operation of the axilla could be avoided in cases of small tumours and a clinically negative axilla. Martelli et al. presented the update of a study including 671 patients ≥ 70 years (172 with axillary dissection and 499 patients without an operation of the axilla) at a median follow up time interval of 15 years. There was no significant difference in mortality within this group in the case of pT1 cN0 disease (10.7% versus 10.7%, $p=0.836$).

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Statement: Treatment according to standard

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Statement: Surgery similar to „younger“ age

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Statement: Endocrine treatment (endocrine resp.)

1. 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
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Statement: Chemotherapy in pts. < 70 years

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Statement: Chemotherapy in pts. > 70 years:

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Statement: Radiotherapy

Recently the long term results of a randomized phase 3 trial investigating the role of radiotherapy in elderly patients with breast conserving was reported. Patients 70 years or older with a clinically negative axilla, T1 tumors, breast conserving surgery, and hormone receptor positive tumor were randomized to Tamoxifen and radiation or to tamoxifen alone. Half of the pts were older than 75 years and around 60 % had no axillary surgery. Distant disease free survival and overall survival at 10 years were without significant difference between the groups. Local relapse was rare however higher in the no radiation arm (Breast: 2% vs 9%; Axilla: 0 % vs 3%).

In a selected low risk population (T1, N0,) in elderly patients (< 70 years) with ER positive disease radiotherapy may be omitted when endocrine treatment with tamoxifen is planned.

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Statement: Trastuzumab

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Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (11/20)

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 circumstances where non-operative therapies or even no treatment may be considered preferable due to these patients' factors and evaluations.

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Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):

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Statement: No axillary clearing (≥ 60 y, cN0, Rec pos)

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2. Martelli G: A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. *Ann Surg*. 2005 Jul;242(1):1-6
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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

1. Du XL, Jones DV, Zhang D. 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.
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Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (12/20)

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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General:

1. Vetto J et al. Accurate and cost-effective evaluation of breast masses in males. Am J Surg 1998 175: 383
2. Heinig J: Clinical management of breast cancer in males: a report of four cases. Eur J Obstet Gynecol Reprod Biol. 2002 Apr 10;102(1):67-73
3. Thalib L ,Hall P. Survival of male breast cancer patients: Population-based cohort study. Cancer Sci. 2008
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Statement: Diagnostic work up as in women

Statement: Mammography

1. Dershaw DD. et al. Mammographic findings in men with breast cancer. Am J Roentgenol 1993 160: 267

2. Hines SL: The role of mammography in male patients with breast symptoms. Mayo Clin Proc. 2007 Mar;82(3):297-300

Statement: Ultrasound

1. Caruso G: High-frequency ultrasound in the study of male breast palpable masses. Radiol Med (Torino). 2004 Sep;108(3):185-93

Statement: Standard-surgery: Mastectomy –men

1. Shen. I et al Skin-sparing mastectomy: a survey based approach to defining standard of care. Am Surg. 2008 Oct;74(10):902-5
2. Lanitis S et al. Diagnosis and management of male breast cancer, World J Surg. 2008 Nov;32(11):2471-6.
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Statement: Sentinel-node excision (SNE)

1. Port ER et al. Sentinel lymph node biopsy in patients with male breast carcinoma. Cancer 2001 91:319-323
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Statement: Radiotherapy as in women (consider tumor breast relation!)

1. Ribeiro GG: A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. Breast 1996; 5: 141-146
2. Schuchardt U et al. Adjuvant radiotherapy for breast carcinoma in men: a 20-year clinical experience. Am J Clin Oncol 1996 19:330
3. Eggemann H et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. Breast Care (Basel). 2013;8(4):270-5.

Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer)

1. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26
2. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 1997; 60: 313-319
3. Basham VM: BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res 2002; 4: R2
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Statement: Screening for 2nd malignancies according guidelines

1. Wernberg JA. Multiple primary tumors in men with breast cancer diagnoses: a SEER database review. J Surg Oncol. 2009 Jan 1;99(1):16-9

Statement: Systemic therapy

1. Doyen J et al., Ann Oncol. 2009 Oct 27. [Epub ahead of print], Aromatase inhibition in male breast cancer patients: biological and clinical implications.
2. Eggemann H et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat. 2013;137(2):465-70.
3. Patten DK et al. New Approaches in the Management of Male Breast. Cancer Clinical Breast Cancer 2013;13(5) 309–314
4. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer Breast Cancer Res Treat. 2013;141(1):119-23
5. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. Br J Cancer. 2013;108(11):2259-63

Review articles

1. Donegan WL: Carcinoma of the breast in males. Cancer 1998; 83: 498-509
2. Borgen PI et al. Current management of male breast cancer. A review of 104 cases. Ann Surg 1992 215:451
3. Erlichman C et al. Male breast cancer: a 13- year review of 89 patients. J Clin Oncol 1984 2: 903
4. Cutuli B, Lacroze M, Dilhuydy JM, et al. Male breast cancer: results of the treatments and prognostic factors in 397 cases. Eur J Cancer 1995; 31A: 1960-1964
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8. Patten DK et al. New Approaches in the Management of Male Breast. Cancer Clinical Breast Cancer 2013;13(5) 309–314

9. Sousa B et al. An update on male breast cancer and future directions for research and treatment. Eur J Pharmacol 2013;717(1-3)
10. Ruddy KJ et al. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. Ann Oncol 2013; 24(6):1434-43.

Male Breast Cancer: Systemic Therapy (13/20)

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.

References:

Statement: Adjuvant Chemotherapy

1. Patel HZ et al. Role of adjuvant chemotherapy in male breast cancer. Cancer 1989 64: 1583
2. Bagley CS et al. Adjuvant Chemotherapy in males with cancer of the breast. Am J Clin Oncol 1987; 2:903

3. Giordano SH, Perkins GH, Broglio K, et al. Adjuvant systemic therapy for male breast cancer. *Cancer* 2005; 104: 235-264
4. Walshe JM: A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up. *Breast Cancer Res Treat.* 2007 Jun;103(2):177-83

Statement Trastuzumab

1. Carmona-Bayonas A. Potential benefit of maintenance trastuzumab and anastrozole therapy in male advanced breast cancer. *Breast.* 2007 Jun;16(3):323-5

Statement endocrine therapy

1. Ribeiro G et al. Adjuvant tamoxifen for male breast cancer (MBC). *Br J Cancer* 1992 65: 252
2. Anelli TF et al. Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. *Cancer* 1994 74: 74
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6. Giordano SH: Efficacy of anastrozole in male breast cancer. *Am J Clin Oncol* 2002 25: 235-237
7. Agrawal A: Fulvestrant in advanced male breast cancer. *Breast Cancer Res Treat.* 2007 Jan;101(1):123. Epub 2006 Jun 29. No abstract available
8. Giordano SH: Leuprolide acetate plus aromatase inhibition for male breast cancer. *J Clin Oncol.* 2006 Jul 20;24(21):e42-3. No abstract available.
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10. Arriola E: Aromatase inhibitors and male breast cancer. *Clin Transl Oncol.* 2007 Mar;9(3):192-4

11. Eggemann H, Ignatov A, Smith BJ, Altmann U, von Minckwitz G, Röhl FW, Jahn M, Costa SD. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013 Jan;137(2):465-70.
12. Di Lauro L et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer *Breast Cancer Res Treat.* 2013;141(1):119-23
13. Zagouri F et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer.* 2013;108(11):2259-63

Statement palliative chemotherapy

1. Chitapanarux I: Gemcitabine plus cisplatin (GC): a salvage regimen for advanced breast cancer patients who have failed anthracycline and/or taxane therapy. *Gan To Kagaku Ryoho.* 2006 Jun;33(6):761-6

Inflammatory Breast Cancer (IBC; cT4d) (14/20)

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:

In case of invasive BC and clinical signs of inflammation (e.g. $\geq 1/3$ of the breast affected) determine stage cT4d

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)). Breast Cancer. Version 1.2016. NCCN.org (Inflammatory Breast Cancer. IBC-1)

Survival benefit by trimodal treatment (NACT, MRM, RT) (LoE 2b B AGO++)

1. Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol* 2014; **32**: 2018–24.

Statement: Staging

1. Yamauchi H et al. Inflammatory breast cancer: what we know and what we need to learn. *Oncologist*. 2012;17(7):891-9. doi: 10.1634/theoncologist.2012-0039. Epub 2012 May 14.
2. S. Dawood et al International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment *Ann Oncol*. 2011 March; 22(3): 515–523
3. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790

Statement: Preoperative chemotherapy

1. Ardavanis A: Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, and Fluorouracil chemotherapy, surgery, and radiotherapy: long-term results. *Oncologist*. 2006 Jun;11(6):563-73
2. S. Johnston (2008), *J. Clin. Oncol.* 26: 1066.1072
3. Mathew J et al. Neoadjuvant chemotherapy for locally advanced breast cancer : A review of the literature and future directions.
4. Schairer C et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. *J Natl Cancer Inst* 2013;105:1373-84.
5. Van Laere et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct affymetrix gene expression datasets. *Clin Cancer Res* 2013;19:4685-96.

Statement: Regimens as in non-inflammatory BC

1. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790

Statement: in HER2 positive disease addition of trastuzumab

1. 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
2. Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, Tjulandin S, Sabadell MD, Caballero A, Valagussa P, Baselga J, Gianni L. 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;37(10):856-6

Statement: in HER2 positive disease addition of trastuzumab and pertuzumab

1. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P. 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 Jan;13(1):25-32. doi: 10.1016/S1470-2045(11)70336-9. Epub 2011 Dec 6.

Statement: in HER2 negative disease addition of bevacizumab

1. Pierga JY, Petit T, Delozier T, et al. Neoadjuvant bevacizumab, trastuzumab, and chemotherapy for primary inflammatory HER2-positive breast cancer (BEVERLY-2): an open-label, single-arm phase 2 study. *Lancet Oncol* 2012;13(April (4)):375–84.

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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7. Tsai CJ et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed therapy. *Am J Clin Oncol* 2013 [Epub ahead of print].

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

1. Chargari C, Kirova YM, Cottu P, Salmon RJ, Fourquet A Progressive inflammatory breast cancer in patient receiving chemotherapy: The importance of radiotherapy as a part of locoregional treatment. *Radiother Oncol*. 2009 Jan;90(1):160-1. Epub 2008 Sep 2
2. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 2008;72:474–484

Statement: Postoperative systemic therapy as in non-inflammatory BC

1. Veyret C: Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: ten-year results from the French Adjuvant Study Group GETIS 02 Trial. *Cancer*. 2006 Dec 1;107(11):2535-44
2. Low JA: Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. *J Clin Oncol*. 2004 Oct 15;22(20):4067-74.

Reviews

1. Chia S et al. Locally advanced and inflammatory breast cancer *J Clin Oncol* 2008; 26: 786-790
2. Penn CL: Remembering inflammatory breast cancer. Are you up to date on management and treatment? *J Ark Med Soc*. 2007 Oct;104(4):80-2.
3. Cristofanilli M: Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer*. 2007 Oct 1;110(7):1436-44
4. Brouwers B et al. Clinicopathological features of inflammatory versus noninflammatory locally advanced nonmetastatic breast cancer
5. Dawood S, Merajver SD, Viens P, Vermeulen PB, Swain SM, Buchholz TA, Dirix LY, Levine PH, Lucci A, Krishnamurthy S, Robertson FM, Woodward WA, Yang WT, Ueno NT, Cristofanilli M. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. *Ann Oncol*. 2011;22(3):515-23.
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Benefit from Trimodal Treatment in Inflammatory Breast Cancer (15/20)

Further information and references:

Survival benefit by trimodal treatment (NACT, MRM, RT) (LoE 2b B AGO++)

1. Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol* 2014; **32**: 2018–24.

Axillary Metastasis in Carcinoma of Unknown Primary (CUP) (16/20)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in $\leq 75\%$ of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management. Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial. (Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85) MRI is also reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour. (Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8) All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinalysis, fecal occult blood test. Jerusalem G: Ann Oncol 17 (Suppl 10) 2006:168-176) The appropriate treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal AH: Am J Surg. 2005 Oct;190(4):609-13) Probably these patients need to be treated as typical stage II patients. (Matsuoka, K: Breast Cancer. 2003;10(4):330-4 / Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005) The management of axillary node metastases in women with adenocarcinoma should be the same as the management of patients with lymph node metastases in breast cancer. If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed. (Buqat R: Bull Cancer. 2002 Oct;89(10):869-75).

The radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unknown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C/+/-.]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% ($p < 0,001$) [Barton et al., 2011].

A systematic review of 24 retrospective studies enrolling 689 patients with axillary metastases of unknown origin showed that axillary CUP is associated with similar presentation, biology and outcome to node positive overt breast cancer and should be treated accordingly.

References:

1. Greco FA, Pavlidis N. Treatment for patients with unknown primary carcinoma and unfavorable prognostic factors. *Semin Oncol.* 2009;36:65–74

Statement: Mammography / Breast ultrasound/ Breast MRI

1. Lalonde L: *Can Assoc Radiol J.* 2005 Dec;56(5):301-8
2. Ko EY: Breast MRI for evaluating patients with metastatic axillary lymph node and initially negative mammography and sonography. *Korean J Radiol.* 2007 Sep-Oct;8(5):382-9

Statement: Staging

1. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. *Breast.* 2005 Apr;14(2):165-8
2. Jerusalem G: *Ann Oncol* 17 (Suppl 10) 2006: 168-176
3. Hemminki K, et al. Site-specific cancer deaths in cancer of unknown primary diagnosed with lymph node metastasis may reveal hidden primaries. *Int J Cancer* 2013; 132:944-50.

Statement: PET

4. Kwee Th.et al:This article Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis *Eur Radiol.* 2009 March; 19(3): 731–744.
5. Varadhachary GR: *Cancer.* 2004 May 1;100(9):1776-85
6. Pelosi E: *Q J Nucl Med Mol Imaging.* 2006 Mar;50(1):15-22.

Statement: Gene expression profiling

1. Bender RA, Erlander MG. Molecular classification of unknown primary cancer. *Semin Oncol.* 2009;36:38–43.
2. Gauri et al., *JCO*, 26:4442-8, 2008;

3. Horlings et al., JCO, 26: 4435-4441, 2008
4. Pentheroudakis G, et al. Global microRNA profiling in favorable prognosis subgroups of cancer of unknown primary (CUP) demonstrates no significant expression differences with metastases of matched known primary tumors. Clin Exp Metastasis 2013; 30:431-9

Statement: ER, PR, HER2

1. Jue Wang et al Occult Breast Cancer Presenting as Metastatic Adenocarcinoma of Unknown Primary: Clinical Presentation, Immunohistochemistry, and Molecular Analysis Case Rep Oncol. 2012 Jan-Apr; 5(1): 9–16. F.
2. Anthony Greco et al Molecular Profiling in Unknown Primary Cancer: Accuracy of Tissue of Origin Prediction Oncologist. 2010 May; 15(5): 500–506.

Statement: Axillary dissection

1. Bugat R: Bull Cancer. 2002 Oct;89(10):869-75
2. Steunebrink: Bilateral axillary metastases of occult breast carcinoma: report of a case with a review of the literature. Breast. 2005 Apr;14(2):165-8
3. Pentheroudakis G et al. Axillary node metastases from carcinoma of unknown primary (CUPax): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119:1-11
4. Schmidt T, Ulrich A. [Surgical options in cancer of unknown primary (CUP)]. Radiologe. 2014 Feb;54(2):140-4.

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
5. Schmidt T, Ulrich A. [Surgical options in cancer of unknown primary (CUP)]. Radiologe. 2014 Feb;54(2):140-4.

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 (17/20)

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)

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.

Statement: Paget's disease with underlying disease (e.g. invasive breast cancer, DCIS): therapy according to standard of the underlying disease

1. 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(18/20)

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:

In general

Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, Calvo JP, Dabbs DJ, Ellis IO, Eusebi V, Farshid G, Fox SB, Ichihara S, Lakhani SR, Rakha EA, Reis-Filho JS, Richardson AL, Sahin A, Schmitt FC, Schnitt SJ, Siziopikou KP, Soares FA, Tse GM, Vincent-Salomon A, Tan PH. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016 Jan;68(1):5-21.

Statement: Core biopsy

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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.

Statement: Complete (wide) local excision or MRM (LoE: 2c):

References 1-4 (retrospective analysis , case reports)

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Statement: SNE / Axillary dissection in cN0 (LoE: 4):

References 1-3 (retrospective analysis, case reports)

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2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94
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Statement: Staging (LoE 5 D AGO+/-)

Note: In malignant phyllodes tumours, the risk of developing of metastases has been described between 10% and 35%, mean 17%; some authors with larger series (Belkacemi et al.2008) observed only 3.4% in their series.

Therefore, patients with benign phyllodes tumours do not need extensive staging diagnostics, patients with malignant phyllodes tumours having residual tumour after surgery or having a high proliferation rate (>5 mitotic counts) an higher rate of recurrences has been observed, however, most often as local recurrences. In benign phyllodes tumours, distant metastases are unknown, whilst in borderline lesions also distant metastases may occur, but less frequent than in malignant disease. In summary, as in breast cancer, clinical staging may be worthwhile, a additional impact by regular imaging including PET and MRI in the follow-up has not been shown.

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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

3. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, Calvo JP, Dabbs DJ, Ellis IO, Eusebi V, Farshid G, Fox SB, Ichihara S, Lakhani SR, Rakha EA, Reis-Filho JS, Richardson AL, Sahin A, Schmitt FC, Schnitt SJ, Siziopikou KP, Soares FA, Tse GM, Vincent-Salomon A, Tan PH. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016 Jan;68(1):5-21.
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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
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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
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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)

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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,
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Statement: Treatment of local recurrence => R0 Resection: LoE: 4; References (retrospective analysis , case reports)

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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 C 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 (19/20)

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:

In general

1. Lim SZ, Ong KW, Tan BK, Selvarajan S, Tan PH. Sarcoma of the breast: an update on a rare entity. J Clin Pathol. 2016 Jan 4. pii: jclinpath-2015-203545.

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).

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Sarcoma / Angiosarcoma of the Breast Local recurrences and metastases (20/20)

No further information

References:

Hyperthermia:

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Breast Cancer Follow-Up

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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 | 2b | B | + |
| ➤ Improve physical performance | 2b | B | + |
| ➤ Reduce therapy related side effects
as osteoporosis, cardiac failure, fatigue,
neurotoxicity, lymphedema, sexual disorders,
cognitive impairment | 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)

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
- **Avoid 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 before** 1b A ++

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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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
- DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI

Oxford / AGO LoE / GR

1a	A	++
1a	B	++
5	D	+
1a	A	++
2a	B	++
3b	B	+/-
3b	B	+
5	D	++
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 +/-

Early Detection of Potentially Curable Events

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Contralateral breast cancer:

- Rel. risk: 2,5–5
- Incidence: 0,5–1,0 % / year
- **Breast self-examination**
- **Physical examination, mammography & US**
- **Routine breast MRI**

5	D	+
1a	A	++
5	D	-

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Early Detection of Potentially Curable Events

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Unrelated site carcinoma:

- Colon RR 3,0; endometrium RR 1,6
ovary RR ca. 1,5; lymphoma RR 7
- Screening for secondary malignancies
according to current guidelines ++
- Pelvic examination and PAP smear 5 D ++
- Routine endometrial ultrasound / biopsy 1b B -

Follow-Up Care for Breast Cancer

Recommendations for asymptomatic pts.

(modified ASCO-ACS guidelines 2016, NCCN 1.2016 guidelines 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
Self-examination		monthly					
Imaging modalities and biochemistry		indicated only by complaints, clinical findings or suspicion of recurrence					
Mammo- graphy and sono- graphy	BCT**	ipsilat.: every 12 months contralat.: every 12 months			on both sides: every 12 months		
	Mastectomy	contralateral every 12 months					

* Continued follow-up visits if still on adjuvant treatment

** In pts with breast-conserving therapy (BCT): First mammography 1 year after initial mammography or at least 6 months after completion of radiotherapy

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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Breast Cancer Follow-Up (2/16)

No further information

No references

Breast Cancer Follow-Up, Objectives I (3/16)

No further information

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Statement: risk factors of mortality after loco-regional recurrence

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Breast Cancer Follow-Up, Objectives II (4/16)

No further information

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Statement: Obesity, physical activity and quality of life

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Breast Cancer Follow-Up, Objectives III (5/16)

No further information

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Statement: Re-evaluation of current adjuvant therapy

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Statement: Monitoring of compliance

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Breast Cancer Follow-Up, Objectives (6/16)

No further information

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Statement: Early Detection

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Statement: prophylactic surgery

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Breast Cancer Follow-Up, Objectives (7/16)

No further information

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Statement: Early Detection

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Statement: Psycho-social aspects

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Statement: for all statements see most recent literature see at Survivorship care guidelines of ASC and ASCO :

1. Runowcz CD, Leach CR, Henry L et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline CA Cancer J Clin 2016; 66: 43-73

Follow-up Objectives - Reported by Patients (8/16)

No further information

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Routine Follow-Up Examinations in Asymptomatic Patients (9/16)

No further information

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Statement: History (specific symptoms)

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Statement: Physical examination

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Statement: Breast self-examination

Expert Opinion

Statement: Mammography

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Statement: Sonography of the breast

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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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Statement: DEXA scan

Expert Opinion

1. Runowicz CD, Leach CR, Henry L et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *CA Cancer J Clin* 2016; 66: 43-73

Routine Follow-Up Examinations in Asymptomatic Patients (10/16)

No further information

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Statement: Magnetic resonance imaging (MRI) of the breast

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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

1. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distant V (for the National Research Council Project on Breast Cancer Follow-up) (1994) Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 271: 1593–1597
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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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Statement: Whole body MRI

1. Vranjesevic D, Filmont JE, Meta J, Silverman DH, Phelps ME, Rao J, Valk PE, Czernin J. Whole-body (18)F-FDG PET and conventional imaging for predicting outcome in previously treated breast cancer patients. J Nucl Med. 2002 Mar;43(3):325-9.
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Early Detection of Potentially Curable Events (11/16)

No further information

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Statement incidence

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Statement breast self examination

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Statement physical examination, mammography & US

1. Montgomery DA, Krupa K, Cooke TG: Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. *Br J Cancer*. 2007 Dec 17;97(12):1632-41.
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Early Detection of Potentially Curable Events (12/16)

No further information

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Statement risk and incidence

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Statement breast self examination

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Statement physical examination, mammography & US

1. Montgomery DA, Krupa K, Cooke TG: Follow-up in breast cancer: does routine clinical examination improve outcome? A systematic review of the literature. Br J Cancer. 2007 Dec 17;97(12):1632-41.
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Statement: Risk according to intrinsic subtype

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No further information

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Statement: Pelvic examination and PAP smear

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Statement: Marrow neoplasms after adjuvant breast cancer therapy

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Follow-Up Care for Breast Cancer (14/16)

No further information

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Breast Cancer Follow-up - Duration. Breast Nurses. (15/16)

No further information

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Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients (16/16)

No further information

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Loco-regional Recurrence



Loco-regional Recurrence

- **Version 2002:**
Brunnert / Simon
- **Versions 2003–2015:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Harbeck / Lisboa /
Maass / Mundhenke / Rezai / Solomayer /
Souchon / Thomssen**
- **Version 2016:**
Rezai / Budach / Wenz

Loco-regional Recurrence Incidence and Prognosis

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
- Reassessment of ER, PR, HER2
- Complete re-staging

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5	D	++
3b	B	++
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

- | | |
|---|-----|
| ➤ 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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Metaanalysis: 7174 BCT and 5418 ME

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

After BCT:

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

After ME:

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

Result:

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

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References

Loco-regional Recurrence Prognostic / Predictive factors

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Parameters in local recurrence to define risk for re-recurrence

- | | | |
|-----------------|----|---|
| ➤ Tumor size | 2a | B |
| ➤ Multifocality | 2a | B |
| ➤ Localisation | 2b | B |

Parameters in local recurrence to define risk for distant metastasis/survival

- | | | |
|---|----|---|
| ➤ Early (<2-3 yrs.) vs. late recurrence | 2b | B |
| ➤ LVSI/Grade/ERneg/positiv margin
(if ≥ 2 factors pos.) | 3b | B |

Predictive factors for treatment considerations

- | | | | |
|--------------|----|---|----|
| ➤ 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

Ipsilateral Recurrence after BCT Surgery

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- **Mastectomy (aim: R0)**
- **Re-BCS with tumor-free margins**
- **Axillary intervention after prior AxDissection if cN0**
- **SNE after prior SNE if cN0**
- **Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial)**

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3b	B	++
3b	C	+/-
4	C	-
1b	B	+/-
5	D	+

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*If no sentinel lymph node can be identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

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➤ **Curative situation: R0-resection**

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2b **A** **++**

➤ **Palliative situation: Resection of
deep parts of the chest wall**

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

➤ **Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial)**

5 **D** **+**

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Loco-regional Recurrence after R0-Resection

Systemic Treatment

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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 (consider neoadjuvant) | 2b | B | + |
| ➤ In case of HER2 positive disease
Chemotherapy + HER2 targeted therapy | 5 | D | + |

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Chemo Therapy by Loco-regional Recurrence

➤ 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).

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 | ++ |

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:

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Lin NU, Thomssen C, Cardoso F, Cameron D, Cufer T, Fallowfield L, Francis PA, Kyriakides S, Pagni O, Senkus E, Costa A, Winer EP: European School of Oncology-Metastatic Breast Cancer Task Force. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013 Jun;22(3):203-10.

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:viii11-9, 2012

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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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HER-2 positive breast cancer is associated with an increased risk of positive cavity margins after initial lumpectomy
Haixia Jia, Weijuan Jia, Yaping Yang, Shunrong Li, Huiyi Feng, Jieqiong Liu, Nanyan Rao, Liang Jin, Jiannan Wu, Ru Gu, Liling Zhu, Kai Chen, Heran Deng, Yunjie Zeng, Qiang Liu, Erwei Song, and Fengxi Su
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HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Jia WJ1, Jia HX, Feng HY, Yang YP, Chen K, Su FX.

Statement: Grading (G3 vs. G1)

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Statement: pT (> 2 vs. ≤ 2cm)

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[Local recurrence based on size after conservative surgery in breast cancer stage T1-T2. A population-based study]. [Article in Spanish] Martínez-Ramos D1, Fortea-Sanchis C2, Escrig-Sos J2, Prats-de Puig M3, Queralt-Martín R2, Salvador-Sanchis JL
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Locoregional recurrence risk factors and the impact of postmastectomy radiotherapy on patients with tumors 5 cm or larger. Nagao T1, Kinoshita T, Tamura N, Hojo T, Morota M, Kagami Y. Author information 1 Department of Breast Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

Statement: pN (N1 vs. N0)

1. 7 Cir Cir. 2014 May-Jun;82(3):252-61.
[Local recurrence based on size after conservative surgery in breast cancer stage T1-T2. A population-based study]. [Article in Spanish] Martínez-Ramos D1, Fortea-Sanchis C2, Escrig-Sos J2, Prats-de Puig M3, Queralt-Martín R2, Salvador-Sanchis JL

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

1. Saigal K, Hurley J et al. Risk factors for locoregional failure in patients with inflammatory breast cancer treated with trimodality therapy. Clin Breast Cancer 13:335-43, 2013

Statement: Nomograms

1. Tsoutsou PG, Jeanneret Sozzi W et al. Nomograms predicting locoregional recurrence in the subtype era of breast cancer. J Clin Oncol 31: 647-8, 2013
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Statement: Obesity

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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
2. Lannin DR, Haffty BG. End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

Statement: Multifocality

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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
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Statement: Early vs. Late recurrence

1. Lee JS, Kim SI, Park HS, Lee JS, Park S, Park BW. The impact of local and regional recurrence on distant metastasis and survival in patients treated with BCT. J Breast Cancer 14:191-7, 2011
2. Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 23(2):285-91, 1992
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LVSI/Grade/ERneg/close margins

Change from close margin to positive margin

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2. Margin width and Re-excision in breast conservativ treatment. a Denish breast coopertive group of 11.900 women. A. Bodilson et all St Antonio Breast cancer symposium Dez.2015. Increased risk of IBTR associated with final positive margin.

Predictive factors for treatment considerations

Statement: HER-2

1. Clemons M, Hamilton T, Goss P. Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001

Statement: ER and PR

1. Clemons M, Hamilton T, Goss P. Does treatment at the time of locoregional failure of breast cancer alter prognosis? *Cancer Treat Rev* 27(2): 83–97, 2001
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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.

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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
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3. Int J Surg. 2015 Nov;23(Pt A):141-6. doi: 10.1016/j.ijsu.2015.08.084. Epub 2015 Oct 9. Surgical management of ipsilateral breast tumor recurrence. Kolben T1, Schwarz TM2, Goess C2, Blume C2, Degenhardt T2, Engel J3, Wuerstlein R2, Ditsch N2, Harbeck N2, Kahlert S2.
4. NCCN clinical practice Guidelines in oncology(NCCN guidelines) breast cancer Version 3.2015 NCCN.org

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
3. Int J Surg. 2015 Nov;23(Pt A):141-6. doi: 10.1016/j.ijsu.2015.08.084. Epub 2015 Oct 9.
Surgical management of ipsilateral breast tumor recurrence. Kolben T1, Schwarz TM2, Goess C2, Blume C2, Degenhardt T2, Engel J3, Wuerstlein R2, Ditsch N2, Harbeck N2, Kahlert S2.
4. Breast Tumor Recurrence J Surg Oncol 2014;110:62–67. Vila J, Garcia-Etienne CA, Vavassori A, Gentilini O. Conservative Surgery for Ipsilateral

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]
9. *Ann Surg Oncol.* 2015 Dec 7. [Epub ahead of print]
Reoperative Sentinel Lymph Node Biopsy is Feasible for Locally Recurrent Breast Cancer, But is it Worthwhile?
Ugras S1, Matsen C1,2, Eaton A3, Stempel M1, Morrow M1, Cody HS 3rd4.

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. Easson AM, McCready DR: Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
2. 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.

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 Radiation Oncology Biol Phys* 72: 1456-64, 2008.
4. 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.

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.
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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
4. 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
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
6. Linthorst M, van Geel AN, Baaijens M, et al. Re-irradiation and hyperthermia after pulsed dose rate (PDR) brachytherapy moulds for breast cancer local recurrences. *Int J Radiat*
7. *Surgery for recurrent breast cancer* . *Radiother Oncol* 2013;109:188-93
8. Linthorst M, van Geel AN, Baartman EA, et al. Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. *Strahlenther Onkol* 2013;189:387-393

Statement: Curative situation: irradiation of the chest wall +/- regional lymph nodes

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. *Int J Radiat Oncol Biol Phys*. 2007 Sep 13

Chest-wall recurrence / Axillary recurrence - radiotherapy (17/18)

No further information

References:

Statement: If no prior postmastectomy radiotherapy

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. Int J Radiat Oncol Biol Phys 70(2):477-84, 2008

Statement: Re-irradiation (chest wall + hyperthermia)

1. Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL.: Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: a review of the randomised data. Int J Hyperthermia 26(7):612-7, 2010
2. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, van Putten WLJ, van Rhoon GC, van Dijk JDP, Gonzalez Gonzalez D, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: Results from five randomized controlled trials. Int J Radiat Oncol Biol Phys 35:731–744, 1996

Statement Axillary recurrence

1. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17; Version 3.2012
2. Konkin DE, Tyldesley S, Kennecke H, Speers CH, Olivotto IA, Davis N Arch Surg. Management and outcomes of isolated axillary node recurrence in breast cancer 141(9):867-72, 2006

3. Ishitobi M, Matsushita A, T Nakayama, et al. Regional lymphatic recurrence after salvage surgery for ipsilateral breast tumor recurrence of breast cancer without local treatment for regional lymphatic basin. J Surg Oncol 2014;110:265-269

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
11. Linthorst M, Baaijens M, Wiggendaad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Radiother Oncol 2015; May 19

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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Endocrine and “Targeted” Therapy in Metastatic Breast Cancer

Endocrine Therapy of Metastatic Breast Cancer

➤ **Version 2002:**

Gerber / Friedrichs

➤ **Versions 2003–2015:**

**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat / Kaufmann /
Liedtke / Loibl / Lück / von Minckwitz / Möbus /
Müller / Mundhenke / Nitz / Schneeweiß /
Schütz / Stickeler**

➤ **Version 2016:**

Hanf / Mundhenke

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
(or unknown) hormone receptor (HR) status.**

- **Exception: acute life-threatening disease**
- **Caveat: HR might change during the course of disease. Histology of recurrent site should be obtained whenever possible**

Comparison ER/PR and HER2 Metastasis vs. Primary Tumor

Meta-analysis 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 tumors 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

Endocrine Therapy

General considerations

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Within all lines of treatment, treatment options should take previous endocrine therapies, age and comorbidities into consideration as well as respective approval status

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Further
Information

References

Endocrine Therapy

in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

	Oxford / AGO LoE / GR		
➤ GnRHa + tamoxifen (vs. OFS or Tam)	1a	A	++
➤ Ovarian function suppression (OFS)	2b	B	+
➤ Tamoxifen	2b	B	+
➤ GnRHa + AI (first or second line)	2b	B	+
➤ GnRHa + Fulvestrant	1b	B	+
➤ GnRHa + Fulvestrant + Palbociclib	1b	B	+
➤ Aromatase inhibitors without OFS	3	D	--

Endocrine Therapy

in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

*There is no evidence for superiority of a single aromatase inhibitor.
As everolimus plus exemestane is indicated after AI treatment, a
non-steroidal AI should be preferred in first line. MA[§]: Megestrole-
acetate, ** steroidal or non-steroidal resp. depending on previous AI

- **Fulvestrant 500 mg**
- **Aromatase inhibitors** (3rd gen) **
- **Tamoxifen**
- **Letrozole + Palbociclib**
- **Fulvestrant 500 mg plus Palbociclib**
- **Exemestane + Everolimus**
- **Tamoxifen + Everolimus**
- **MPA/MA[§]**
- **Fulvestrant 250 mg + Anastrozol**
- **Estradiol valerate 2-6 mg daily**
- **Repeat prior treatments**

Oxford / AGO LoE / GR

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

Therapy Algorithm After Adjuvant Tamoxifen

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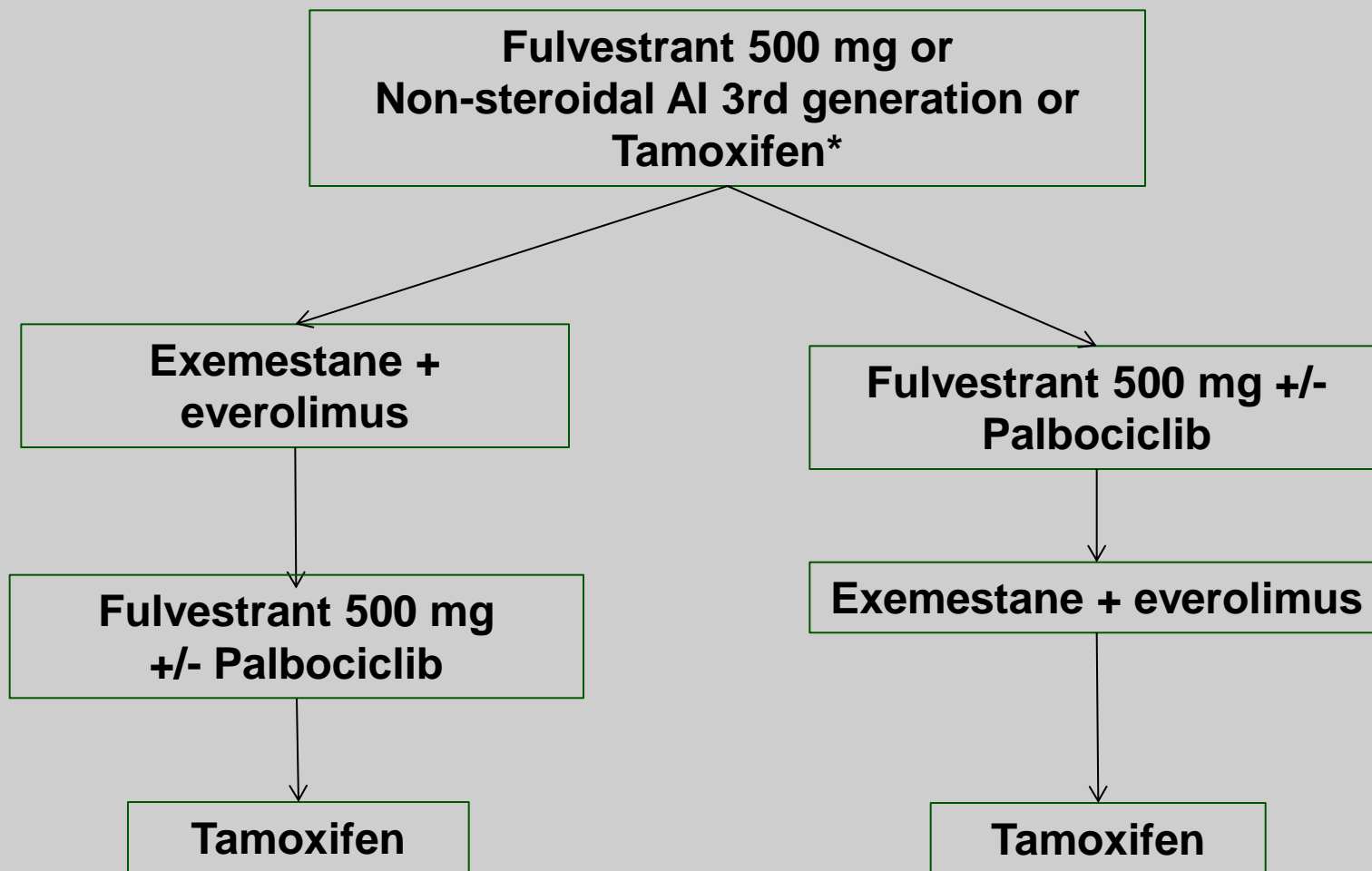
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Information

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LEHREN
HEILEN

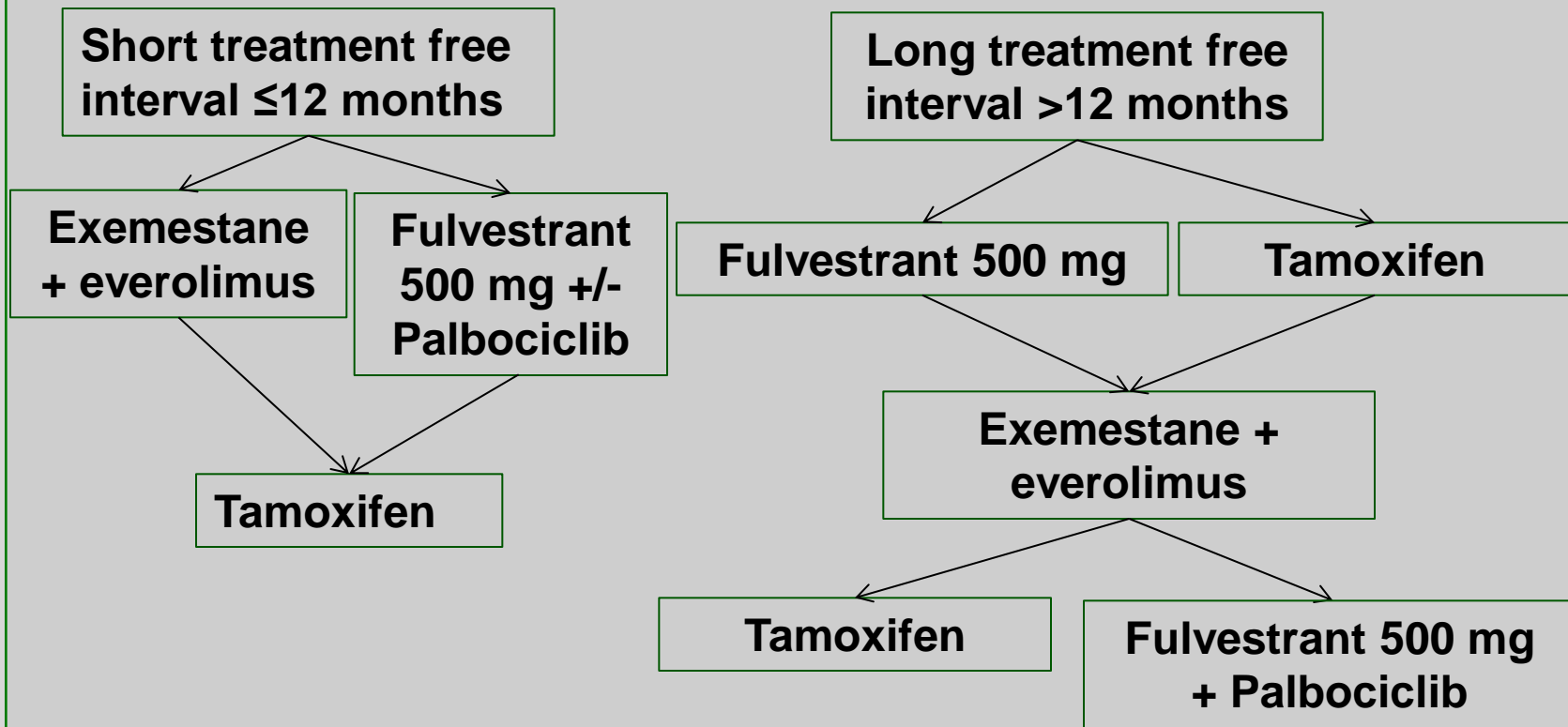


*(after long recurrence-free intervall)

Therapy Algorithm After Adjuvant AI

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Further
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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 B +

1b B -

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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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LoE / GR

- | | | | |
|---------------------------------------|-----------|----------|------------|
| ➤ Anastrozole plus trastuzumab | 1b | B | +/- |
| ➤ Letrozole plus trastuzumab | 2b | B | +/- |
| ➤ Letrozole plus lapatinib | 1b | B | +/- |
| ➤ Fulvestrant plus lapatinib | 1b | B | +/- |

Poor efficacy of endocrine therapy alone.

Consider induction chemotherapy + anti-HER2-therapy!

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Further
Information

References

Combination of Endocrine Treatment with Anti-HER2-Treatment

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Treatment (no. of pats)	PFS (months)	Response rate (CBR)	OS (months)
Trastuzumab + anastrozole vs. anastrozole (n=207)	4.8 vs. 2.4 (5.6 vs. 3.8 with centrally 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%	not reported
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=146/145)	4.1 vs. 3.8 (HER2-) p: 0,25 5.9 vs. 3.3 (HER2+) p: 0,53	(CR +PR) 20 vs. 9% p: 0,048	30 vs. 26.4 mo (all), n.s.

Concomitant or Sequential Endocrine-Cytostatic Treatment

Oxford / AGO
LoE / GR

- **Concomitant endocrine-cytotoxic treatment**
- **May increase response rate and progression free interval but not overall survival**
 - **May increase toxicity**
- **Maintenance endocrine therapy after chemotherapy induced response**
 - **Increases progression free interval**

1b A -

2b B ++

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Endocrine and “Targeted” Therapy in Metastatic Breast Cancer (2/14)

No further information

No references

Endocrine and “Targeted” Therapy in Metastatic Breast Cancer (3/14)

No further information

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Comparison ER/PR and HER2 Metastasis vs. Primary Tumor (4/14)

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Endocrine Therapy General Considerations (5/14)

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Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (6/14)

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Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (7/14)

No further information

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Fulvestrant 500 mg

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Therapy Algorithm after Adjuvant Tamoxifen (8/14)

No further information

No references

Therapy Algorithm after Adjuvant AI (9/14)

No further information

No references

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No further information

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No further information

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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 START

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*Substances are only discussed if there is at least published evidence
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 2003–2015:**
**Bischoff / Dall / Fersis / Friedrichs / Harbeck /
Jackisch / Janni / Möbus / Müller / Scharl /
Schmutzler / Schneeweiss / Schütz / Stickeler /
Thomssen / von Minckwitz**

- **Version 2016:**
Thill / Rody

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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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Endocrine Resistance in Metastatic Breast Cancer

Primary endocrine resistance:

**Relapse while on the first 2 years of adjuvant ET,
Or PD within first 6 months of first-line ET for MBC,
while on ET**

Secondary endocrine resistance:

**Relapse while on adjuvant ET but after the first 2 years,
or a relapse within 12 months of completing adjuvant
ET, or PD \geq 6 months after initiating ET for MBC,
while on ET**

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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	++
Bisphosphonates	bone 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**

2b B +

➤ **Treatment until best response**

2b B +/-

➤ **Change to alternative regimen
before progression**

2b B +/-

➤ **Stop therapy in case of**

1c A ++

➤ **Progression**

➤ **Non tolerable toxicity**

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Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends on:

- **ER / PR, HER2; combination with biologicals**
- **Previous treatments (and their toxicities)**
- **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

Taxane-containing Regimens for Metastatic Breast Cancer

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Gherzi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 Jun 10;6:CD003366.

See: Forest plot of comparison: I Overall survival, outcome: I.I Overall effect: Taxane-containing regimes vs. not

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MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

Oxford / AGO
LoE / GR

➤ Paclitaxel q1w	1a	A	++
➤ Docetaxel q3w	1a	A	++
➤ Capecitabine	2b	B	++
➤ Nab-paclitaxel	2b	B	++
➤ Peg-liposomal doxorubicin	2b	B	+
➤ Eribulin	1b	B	+
➤ Vinorelbine	2b	B	+
➤ Docetaxel + Peg-liposomal Doxo	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	+
➤ Taxane re-challenge	2b	B	+
➤ Anthracycline re-challenge	3b	C	+
➤ Metronomic therapy (eg. cyclophos. + MTX)	2b	B	+
➤ Gemcitabine + Cisplatin / Carboplatin	2b	B	+/-
➤ Gemcitabine + Capecitabine	2b	B	+/-
➤ Gemcitabine + Vinorelbine*	1b	B	-

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 +

1b B +

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

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	Oxford / AGO LoE / GR		
➤ Docetaxel + trastuzumab + pertuzumab	1b	A	++
➤ Paclitaxel (wk) + trastuzumab + pertuzumab	2b	B	+
➤ Vinorelbine + Trastuzumab + Pertuzumab	3b ^a	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	B	+/-
➤ Taxanes + trastuzumab + everolimus	1b	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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➤ 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

Oxford / AGO
LoE / GR

Pretreatment with Trastuzumab

- T-DM 1
- Capecitabine + lapatinib
- Vinorelbine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Chemotherapy + trastuzumab + („treatment beyond progression“)
 - Trastuzumab + pertuzumab
 - Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)

1b	A	++
1b	B	+
2b	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	+
5	D	

For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.

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
- Vinorelbine
- AI in ER positive disease

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

- In patients with brain metastases (radioresistance) in combination with capecitabine

2b	B	+/-
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Immunodiagnostic Tests and Immunotherapy*

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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;...)**

*Study participation recommended

Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/20)

No further information

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, 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). Ann Oncol. 2014;25:1871-88.u

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 (3/20)

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.

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.

Endocrine resistance in metastatic breast cancer (4/20)

No further information

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.u

Treatment of Metastatic Breast Cancer - Predictive Factors (5/20)

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.
2. Smerage JB, Barlow WE, Hortobagyi GN, Winer EP, Leyland-Jones B, Srkalovic G, Tejwani S, Schott AF, O'Rourke MA, Lew DL, Doyle GV, Gralow JR, Livingston RB, Hayes DF. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol.* 2014 Nov 1;32(31):3483-9.

Cytotoxic Therapy Goals (6/20)

No further information

References:

1. (O'Shaugnessy et al, 2003, Albain, 2004)
2. (Sledge et al, 2003).

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

Metaanalysis

Docetaxel alone or in combination

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.

Cochrane analysis

1. Carrick S, Parker S, Thornton CE, Gherzi D, Simes J, Wilcken N. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD003372. doi: 10.1002/14651858.CD003372.pub3. Review.

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 (7/20)

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 (8/20)

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, Freudenstrung 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 E, Ruiz-Borrego M, Margelí M, Rodríguez-Lescure A, Sánchez-Rovira P, Ruiz A, Mel-Lorenzo JR, Ramos-Vázquez M, Ribelles N, Calvo E, Casado A, Márquez A, Vicente D, García-Sáenz JA, Martín M. Maintenance

treatment with pegylated liposomal doxorubicin versus observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study. Breast Cancer Res Treat. 2010 Jul;122(1):169-76

3. Park YH, Jung KH, Im SA, Sohn JH, Ro J, Ahn JH, Kim SB, Nam BH, Oh do Y, Han SW, Lee S, Park IH, Lee KS, Kim JH, Kang SY, Lee MH, Park HS, Ahn JS, Im YH .Phase III, multicenter, randomized trial of maintenance chemotherapy versus observation in patients with metastatic breast cancer after achieving disease control with six cycles of gemcitabine plus paclitaxel as first-line chemotherapy: KCSG-BR07-02. J Clin Oncol. 2013 May 10;31(14):1732-9.

Chemotherapy for MBC – General Considerations: Drug Selection (9/20)

No further information

References:

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, Carneiro JB, Manunta S, Mazzeo 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 (10/20)

No further information

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).

Individual trials

NabPaclitaxel vs Ixabepilone vs paclitaxel +/- bevacizumab

1. Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Leung E, Mayer EL, Naughton M, Toppmeyer D, Carey LA, Perez EA, Hudis C, Winer EP. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol. 2015 Jul 20;33(21):2361-9

Nab-Paclitaxel

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

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.

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

Cochrane analysis taxane-containing regimens for metastatic breast cancer

1. Gherzi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 Jun 10;6:CD003366.

Taxane-containing Regimens for Metastatic Breast Cancer (11/20)

No further information

No references

MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (12/20)

Further information and references:

Consent: Eribulin: 5++, 21+, 4+/-

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, Bognoux 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.
2. 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, 2015*) 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, 2015; 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.

Nab-paclitaxel

1. Puglisi F, Rea D, Kroes MA, Pronzato P. Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review. *Cancer Treat Rev.* 2016 Feb;43:36-49.

Metaanalysis

1. Cochrane analysis taxane-containing regimens for metastatic breast cancer
Gheri D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev.* 2015 Jun 10;6:CD003366.

MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (13/20)

Further information:

Consent:

Capecitabine/Vinorelbine: ++: 16; +: 2; +/-: 0; -: 0; --: 0
Taxane/anthracycline re-challenge: ++: 1; +: 20; +/-: 6; -: 0; --: 0
Metronomic therapy: ++: 0; +: 13; +/-: 9; -: 0; --: 0

References:

Ixabepilone:

1. Thomas E, Tabernero J, Fornier M, Conté P, Fumoleau P, Lluch A, Vahdat LT, Bunnell CA, Burris HA, Viens P, Baselga J, Rivera E, Guarneri V, Poulart V, Klimovsky J, Lebwohl D, Martin M. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. J Clin Oncol. 2007 Aug 10;25(23):3399-406.
2. Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, Jassem J, Pivot XB, Klimovsky JV, de Mendoza FH, Xu B, Campone M, Lerzo GL, Peck RA, Mukhopadhyay P, Vahdat LT, Roché HH. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007 Nov 20;25(33):5210-7.

Gemcitabine/vinorelbine

1. Martín M, Ruiz A, Muñoz M, Balil A, García-Mata J, Calvo L, Carrasco E, Mahillo E, Casado A, García-Saenz JA, Escudero MJ, Guillem V, Jara C, Ribelles N, Salas F, Soto C, Morales-Vasquez F, Rodríguez CA, Adrover E, Mel JR; Spanish Breast Cancer Research Group (GEICAM) trial. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. *Lancet Oncol.* 2007 Mar;8(3):219-25.
2. Kim JH, Oh SY, Kwon HC, Lee S, Kim SH, Kim DC, Lee JH, Lee HS, Cho SH, Kim HJ. Phase II study of gemcitabine plus cisplatin in patients with anthracycline- and taxane- pretreated metastatic breast cancer. *Cancer Res Treat.* 2008 Sep;40(3):101-5.

Systematic review

1. Puglisi F, Rea D, Kroes MA, Pronzato P. Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review. *Cancer Treat Rev.* 2016 Feb;43:36-49.

Eribulin

Meta-analysis and evaluation

1. Scarpace SL. Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. *Clin Ther.* 2012 Jul;34(7):1467-73.

Phase III trials

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, Bognoux 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.
2. 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.

Taxane re-challenge

1. Guo X, Loibl S, Untch M, Möbus V, Schwedler K, Fasching PA, Barinoff J, Holms F, Thomssen C, Zahm DM, Kreienberg R, Hauschild M, Eidtmann H, Tauchert S, Mehta K, von Minckwitz G. Re-Challenging Taxanes in Recurrent Breast Cancer in Patients Treated with (Neo-) Adjuvant Taxane-Based Therapy. *Breast Care (Basel)*. 2011;6(4):279-283.

Anthracycline re challenge

1. Twelves C, Jove M, Gombos A, Awada A. Cytotoxic chemotherapy: Still the mainstay of clinical practice for all subtypes metastatic breast cancer. *Crit Rev Oncol Hematol*. 2016 Jan 23. pii: S1040-8428(16)30021-X. doi: 10.1016/j.critrevonc.2016.01.021. [Epub ahead of print] Review.

Metronomic chemotherapy

1. Yin W, Pei G, Liu G, Huang L, Gao S, Feng X. Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials. *Oncotarget*. 2015 17;6(36):39365-72.

2. Yoshimoto M, Takao S, Hirata M, Okamoto Y, Yamashita S, Kawaguchi Y, Takami M, Furusawa H, Morita S, Abe C, Sakamoto J. Metronomic oral combination chemotherapy with capecitabine and cyclophosphamide: a phase II study in patients with HER2-negative metastatic breast cancer. *Cancer Chemother Pharmacol*. 2012 Aug;70(2):331-8.
3. Fedele P, Marino A, Orlando L, Schiavone P, Nacci A, Sponziello F, Rizzo P, Calvani N, Mazzoni E, Cinefra M, Cinieri S. Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer. *Eur J Cancer*. 2012 Jan;48(1):24-9.
4. Addeo R, Sgambato A, Cennamo G, Montella L, Faiola V, Abbruzzese A, Capasso E, Leo L, Botti G, Caraglia M, Del Prete S. Low-dose metronomic oral administration of vinorelbine in the first-line treatment of elderly patients with metastatic breast cancer. *Clin Breast Cancer*. 2010 Aug 1;10(4):301-6.
5. Colleoni M, Orlando L, Sanna G, Rocca A, Maisonneuve P, Peruzzotti G, Ghisini R, Sandri MT, Zorzino L, Nolè F, Viale G, Goldhirsch A. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. *Ann Oncol*. 2006 Feb;17(2):232-8.

Gemcitabine + cisplatin / carboplatinum

1. Li HC, Russell CA Gemcitabine and platinum-based chemotherapy in metastatic breast cancer. *Oncology* (Williston Park). 2004 Dec;18(14 Suppl 12):17-22
2. Perez EA Gemcitabine and platinum combinations in patients with breast cancer previously treated with anthracyclines and/or taxanes. *Clin Breast Cancer*. 2004 Jan;4 Suppl 3:S113-6

Review

1. 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-) (14/20)

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. Hu XC, Zhang J, Xu BH, Cai L, Ragaz J, Wang ZH, Wang BY, Teng YE, Tong ZS, Pan YY, Yin YM, Wu CP, Jiang ZF, Wang XJ, Lou GY, Liu DG, Feng JF, Luo JF, Sun K, Gu YJ, Wu J, Shao ZM. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2015 Apr;16(4):436-46.

Triple negative patients

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 (15/20)

Further information and references:

Consent 2014:

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

Individual trials

Taxanes +/- Bevacizumab

NabPaclitaxel vs Ixabepilone vs paclitaxel

1. Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Leung E, Mayer EL, Naughton M, Toppmeyer D, Carey LA, Perez EA, Hudis C, Winer EP. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). *J Clin Oncol*. 2015 Jul 20;33(21):2361-9.

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 (16/20)

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab:	++: 12; +: 13; +/-: 0; -: 0; --: 0
Vinorelbine + trastuzumab – pertuzumab:	++: 0; +: 5; +/-: 17; -: 0; --: 0
Taxanes + lapatinib:	++: 1; +: 3; +/-: 9; -: 4; --: 0
Taxanes + trastuzumab + everolimus:	++: 0; +: 2; +/-: 9, -: 14; --: 0

References:

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.

Docetaxel + trastuzumab + pertuzumab

1. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, Clark E, Ross G, Benyunes MC, Cortés J; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-34.

Pertuzumab side effects

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 weekly + trastuzumab + pertuzumab

1. Dang C, Iyengar N, Datko F, D'Andrea G, Theodoulou M, Dickler M, Goldfarb S, Lake D, Fasano J, Fornier M, Gilewski T, Modi S, Gajria D, Moynahan ME, Hamilton N, Patil S, Jochelson M, Norton L, Baselga J, Hudis C. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015; 10;33(5):442-7.

Vinorelbine + trastuzumab + pertuzumab

1. Michael Andersson, José Manuel López-Vega, Thierry Petit, Claudio Zamagni, Margarita Donica, Julia Kamber, Edith A. Perez. The co-administration of pertuzumab (P) and trastuzumab (T) as a single infusion, followed by vinorelbine (V), in first-line (1L) treatment of HER2-positive locally advanced or metastatic breast cancer (MBC) patients (pts): VELVET study interim analysis. J Clin Oncol 33, 2015 (suppl; abstr 586)

1st line chemotherapy + trastuzumab

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
6. Dang C et al., Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer, J Clin Oncol. 2015 Feb 10;33(5):442-7

Trastuzumab mono

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

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 et al., Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2-Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31, J Clin Oncol. 2015;33(14):1574-83

Taxane + trastuzumab + everolimus

1. Hurvitz SA et al., Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial, Lancet Oncol. 2015 Jul;16(7):816-29

Trastuzumab + aromatase inhibitors (if ER+)

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+)

1. Johnston S, Pippin 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) **(17/20)**

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab: ++: 12; +: 13; +/-: 0; -: 0; --: 0

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. Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, Miles D, Samant M, Welslau M, Diéras V. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann Oncol. 2015 Jan;26(1):113-9.

Capecitabine + lapatinib

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.

When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.

3. 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)

Trastuzumab + lapatinib vs lapatinib

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. Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, Ellis C, Casey M, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010 Mar 1;28(7):1124-30

TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)

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

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

Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab

Trastuzumab mono

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.

Trastuzumab + aromatase inhibitors (if ER+)

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+)

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 (18/20)

Further information:

Consent:

Vinorelbine + lapatinib: ++: 0; +: 4; +/-: 21, -: 1; --: 0

References:

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel)

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
3. André F, O'Regan R, Ozguroglu M, Toi M, Xu B, Jerusalem G, Masuda N, Wilks S, Arena F, Isaacs C, Yap YS, Papai Z, Lang I, Armstrong A, Lerzo G, White M, Shen K, Litton J, Chen D, Zhang Y, Ali S, Taran T, Gianni L. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014 May;15(6):580-91.

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

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.

Vinorelbine + lapatinib

1. Janni W, Sarosiek T, Karaszewska B, Pikiel J, Staroslawska E, Potemski P, Salat C, Brain E, Caglevic C, Briggs K, Mahood K, DeSilvio M, Marini L, Papadimitriou C. Final overall survival analysis of a phase II trial evaluating vinorelbine and lapatinib in women with ErbB2 overexpressing metastatic breast cancer. Breast. 2015 Dec;24(6):769-73.

Trastuzumab + lapatinib (if CT not possible)

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. Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, Ellis C, Casey M, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010 Mar 1;28(7):1124-30

Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1)

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. Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H; TH3RESA study collaborators. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Jun;15(7):689-99.
5. Wildiers H, Kim S-B, Gonzalez-Martin A, LoRusso PM, Ferrero J-M, Yu R, Smitt M, Krop I. Trastuzumab emtansine improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: Final overall survival results from the phase 3 TH3RESA study. San Antonio Breast Cancer Symposium 2015, Abstract S5-05

Lapatinib in HER2-positive Metastatic Breast Cancer (19/20)

No further information

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 JJ, Skarlos D, Newstat B, Roychowdhury D, Paoletti P, Oliva C, Rubin S, Stein S, Geyer CE. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. *Breast Cancer Res Treat.* 2008 Dec;112(3):533-43.
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. Blackwell KL, Burstein HJ, Storniolo AM, Rugo H, Sledge G, Koehler M, Ellis C, Casey M, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010 Mar 1;28(7):1124-30
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

6. Janni W, Sarosiek T, Karaszewska B, Pikiel J, Staroslawska E, Potemski P, Salat C, Brain E, Caglevic C, Briggs K, Mahood K, DeSilvio M, Marini L, Papadimitriou C. Final overall survival analysis of a phase II trial evaluating vinorelbine and lapatinib in women with ErbB2 overexpressing metastatic breast cancer. *Breast*. 2015 Dec;24(6):769-73.

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 (20/20)

No further information

No references

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Bisphosphonates in Metastatic Breast Cancer

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**Oxford / AGO
LoE / GR**

- | | |
|---|----------------|
| ➤ Hypercalcemia | 1a A ++ |
| ➤ Reduction of skeletal events (complications) | 1a A ++ |
| ➤ Reduction of bone pain | 1a A ++ |
| ➤ Increasing bone pain-free survival | 1a A ++ |
| ➤ Treatment beyond progression of bone met's | 5 D ++ |

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Denosumab in Metastatic 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*	1a	A	+
➤	Denosumab 120 mg s.c. q4w	1a	A	++
➤	Denosumab 120 mg s.c. q12w	4	C	-
➤	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.

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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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Further
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References

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-Endoprosthesis**
- **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
- Reduction of radiation induced pain flare by
Dexamethasone

Oxford / AGO LoE / GR

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

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Further
Information

References

FORSCHEN
LEHREN
HEILEN

Only few studies included breast cancer patients!

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	+
➤ Radiofrequency ablation	4	C	+
➤ Cryoablation	4	C	+

***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 Bone Targeted Therapy 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

- **Denosumab (60 mg s.c., q 6mo)**
 - Postmenopausal patients

1a	A	+
1a	B	+/-
1a	A	+
1a	B	+/-
1b ^a	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 -
- **DXA-scan at baseline in pts with AI or with premature menopause** 5 D +
- **Repeat DXA-scan based on risk** 5 D +

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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)

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Medical Treatment of Osteoporosis

Oxford / AGO LoE / GR

➤	Alendronate 70 mg po/w*	1b	B	++
➤	Denosumab 60 mg sc/6m*	1b	B	++
➤	Ibandronate 150 mg po/m*	1b	B	++
➤	Ibandronate 3 mg iv/3m	1b	B	++
➤	Parathyroid hormone (1-84) 100 µg sc/d	1b	B	+
➤	Raloxifene 60 mg po/d (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

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<http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kitteltaschenversion%2015.12.2014.pdf>

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE OSTEOPOROSETHERAPIE 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

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Denosumab in Metastatic Breast Cancer (4/19)

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Metastatic Bone Disease of the Spine – Indication for surgery (7/19)

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Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/19)

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Surgery for Bone Metastases (9/19)

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Metastatic Bone Disease: Radiotherapy (10/19)

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Metastatic Bone Disease Recurrent Bone Pain (11/19)

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Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/19)

Further information:

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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 2003–2015:**
**Bauerfeind / Bischoff / Böhme / Brunnert / Diel /
Fehm / Friedrich / Friedrichs / Gerber / Hanf /
Janni / Lück / Maass / Oberhoff / Rezai /
Schaller / Seegenschmiedt / Solomayer /
Souchon**
- **Version 2016:**
Lux / Schütz

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- **Liver and lung metastases**
- **Malignant pleural and pericardial effusions**
- **Ascites**
- **Bone marrow involvement**
- **Soft tissue metastases**
- **Any other organs**
- **Consider also chapter „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“**

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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, persistance after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression**
- **Systemic treatment after surgery**

**Oxford / AGO
LoE / GR**

3	B	+
2a	B	++*
2b	C	+
3a	B	+
5	D	+/-
5	D	++

*** See chapters with systemic treatment recommendations**

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Further
Information

References

Local Therapy in Primary Metastatic Disease

Oxford / AGO

LoE / GR

- **Local surgical treatment (R0) of primary tumor**
- **Axillary surgery for cN1**
- **Sentinel in cN0**
- **Local radiotherapy of primary tumor**
 - **Alone**
 - **After local surgical treatment with BCS or mastectomy and indication**

1b B +/-

5 C +/-

5 C -

3a C +/-

3a C +

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Liver Metastasis

Local Therapy

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➤ Resection of liver metastasis (R0)

3a B +/-

HR positive: chemotherapy sensitive, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases

HER2 positive: age < 50 y., metastasis < 5 cm, no further metastases

➤ Regional chemotherapy

3b C +/-

➤ Regional radiotherapy

4 C +/-

[SIRT, stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT), radiochemoembolization, other modalities]

➤ Thermoablation

3b C +/-

(RFA, LITT, cryotherapy)

Pulmonary Metastases

Local Therapy

Oxford / AGO

LoE / GR

- **Before surgery: staging and biopsy (fine-needle aspiration with CT-guidance or transbronchial needle aspiration)**

3a B +

- **Resection of pulmonary metastases by VATS or conventional resection**

- In case of multilocular metastatic disease

3a B -

- In case of single metastases on one side with curative intent

3a B +/-

- **Thermoablation (CT-guided RFA, LITT)**

3b C +/-

- **Regional radiotherapy**

4 C +/-

(e.g. stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT))

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 [dyspnea (80%), dull chest pain (30%), nonproductive cough (10%)]
- Survival is related to the presence of additional metastases, age, ECOG PS and extent of involving the pleural surface

Diagnostic procedures:

- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion [cytology (→ 50% false negative), histology by thoracoscopy]

Malignant Pleural Effusion (MPE)

Local Therapy

Oxford / AGO
LoE / GR

- | | | | |
|---|----|---|-----|
| ➤ If expected life time is short, less invasive procedures should be considered | 4 | C | ++ |
| ➤ VATS and Talcum-pleurodesis* | 1b | B | ++ |
| ➤ Chemical pleurodesis* | | | |
| ➤ Talcum powder | 1a | B | + |
| ➤ Bleomycin, Doxycycline, Mitoxantrone | 2b | C | +/- |
| ➤ Povidone-iodine (20 ml of 10% solution) | 1b | B | + |
| ➤ Continous pleural drainage | 2a | B | + |
| ➤ Systemic treatment after pleurodesis | 3b | C | +/- |
| ➤ Local antibody therapy (i.e. Catumaxomab) | 3b | C | - |
| ➤ Serial thoracocentesis | 4 | C | +/- |

* Adequate pain-relief

VATS: video-assisted thoracoscopic surgery

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Malignant Ascites

Local Therapy

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Ascites:

- | | | | |
|--|-----------|----------|------------|
| ➤ Puncture, drainage in symptomatic patients | 4 | D | ++ |
| ➤ Systemic therapy | 3b | D | ++ |
| ➤ Local chemotherapy | 3b | D | +/- |
| ➤ Local antibody therapy (i.e. Catumaxomab) | 3b | D | +/- |

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Malignant Pericardial Effusion

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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 | +/- |

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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

Soft Tissue Metastasis

Local Therapy

Oxford / AGO

LoE / GR

Surgery in locoregional limited metastatic disease (skin, muscular, nodal) in case of complete resection (R0) and no further metastases after staging

4 C +

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 +

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Specific Sites of Metastases (2/13)

No further information

No references

Specific Sites Of Metastases (3/13)

No further information

No references

General Aspects of Metastases Surgery or Ablation (4/13)

No further information

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Local Therapy in Primary Metastatic Disease (5/13)

Further information and references:

Statements:

Local surgical treatment (R0) of primary tumor (1bB +/-)

Statement: Axillary surgery for cN1 (5 C +/-)

Statement: Sentinel in cN0 (5 C -)

Statements:

Local radiotherapy of primary tumour

Alone (3a C +/-)

After local surgical treatment with BCS or mastectomy and indication (3a C +)

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13. Criscitiello C, Giuliano M, Curigliano G, De Laurentiis M, Arpino G, Carlomagno N, De Placido S, Golshan M, Santangelo M. Surgery of the primary tumor in de novo metastatic breast cancer: To do or not to do? *Eur J Surg Oncol.* 2015 Oct;41(10):1288-92. doi: 10.1016/j.ejso.2015.07.013. Epub 2015 Jul 29. Review.

Liver Metastasis - Local Therapy (6/13)

Further information and references:

Vote result of the AGO recommendation (complete slide without further changes): yes = 23/ no = 2

Statements:

Resection of liver metastasis (R0) (3a B+/-)

HR positive: chemotherapy sensible, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases

Her2 positive: age < 50 y., metastasis < 5 cm, no further metastases

1. Furka A, et al: Treatment of liver metastases from breast cancer. Hepatogastroenterology. 2008 Jul-Aug;55(85):1416-8.
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- Surgeons Group Resection of liver metastases in patients with breast cancer: survival and prognostic factors. *Eur J Surg Oncol.* 2012 Oct;38(10):910-7. doi: 10.1016/j.ejso.2012.04.015. Epub 2012 Jun 7.
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 12. Sadot E, Lee SY, Sofocleous CT, Solomon SB, Gönen M, Peter Kingham T, Allen PJ, DeMatteo RP, Jarnagin WR, Hudis CA, D'Angelica MI. Hepatic Resection or Ablation for Isolated Breast Cancer Liver Metastasis: A Case-control Study with Comparison to Medically Treated Patients. *Ann Surg.* 2015 Oct 1. [Epub ahead of print]
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 14. Vertriest C, Berardi G, Tomassini F, Vanden Broucke R, Depypere H, Cocquyt V, Denys H, Van Belle S, Troisi RI. Resection of single metachronous liver metastases from breast cancer stage I-II yield excellent overall and disease-free survival. Single center experience and review of the literature. *Dig Surg.* 2015;32(1):52-9. doi: 10.1159/000375132. Epub 2015 Feb 11.
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Statement: Regional chemotherapy (3b C +/-)

1. Vogl TJ et al. Transarterial chemoembolization (TACE) with mitomycin C and gemcitabine for liver metastases in breast cancer. *Eur Radiol.* 2010;20(1):173
2. Martin RC et al. Optimal outcomes for liver-dominant metastatic breast cancer with transarterialchemoembolization with drug-eluting beads loaded with doxorubicin. *Breast Cancer Res Treat.* 2012;132(2):753-63.

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5. Ang C et al. Hepatic arterial infusion and systemic chemotherapy for breast cancer liver metastases. *Breast J.* 2013;19(1):96-9.
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Statement: Regional radiotherapy (4 C +/-)

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
2. Sofocleous CT et al: Radiofrequency ablation in the management of liver metastases from breast cancer. *AJR Am J Roentgenol.* 2007 Oct;189(4):883-9
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Statement: Thermoablation (3b C +/-)

1. Dwivedi DN, Pal S, Pande GK. Management of liver metastases: cut, cryo, coagulate or chemotherapy. Trop Gastroenterol. 2001 Apr-Jun;22(2):57-64. Review
2. Seifert JK, et al. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature. Technol Cancer Res Treat. 2004 Apr;3(2):151-63.
3. Vogl TJ, et al. MR-guided laser-induced thermotherapy (LITT) of liver tumours: experimental and clinical data. Int J Hyperthermia. 2004 Nov;20(7):713-24
4. Keil S, et al. Radiofrequency Ablation of Liver Metastases-Software-Assisted Evaluation of the Ablation Zone in MDCT: Tumor-Free Follow-Up Versus Local Recurrent Disease. Cardiovasc Intervent Radiol. 2009 Aug 18.
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Pulmonary Metastases Local Therapy (7/13)

Further information and references:

Vote result of the AGO recommendation (complete slide without further changes): yes = 20/ no = 1

Statements:

Before surgery: staging and biopsy (fine-needle aspiration with CT-guidance or transbronchial needle aspiration) (3a B +)

Resection of pulmonary metastases by VATS or conventional resection

In case of multilocular metastatic disease (3a B -)

In case of single metastases on one side with curative intent (3a B +/-)

1. Tanaka F, et al: Surgery for pulmonary nodules in breast cancer patients. Ann Thorac Surg. 2005 May;79(5):1711-4; discussion 1714-5.
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3. Welter S, et al: Pulmonary metastases of breast cancer. When is resection indicated? Eur J Cardiothorac Surg. 2008 Dec;34(6):1228-34.
4. Erhunmwunsee L, D'Amico TA Surgical management of pulmonary metastases. Ann Thorac Surg. 2009 Dec;88(6):2052-60
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Statement: Thermoablation (CT-guided RFA, LITT) (3b C +/-)

1. Vogl TJ, et al: Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. *Radiology*. 2011 Nov;261(2):643-51.
2. Ewert R, Opitz C. Pulmonary function testing before ablative methods] *Radiologe*. 2004 Jul;44(7):708-10. 4.
3. Diederich S, Hosten N: Percutaneous ablation of pulmonary tumours: state-of-the-art 2004 *Radiologe*. 2004 Jul;44(7):658-62.

Statement: Regional radiotherapy (4 C +/-)

1. Louie J, et al.: Radio frequency ablation of lung metastasis using sonographic guidance. *J Ultrasound Med*. 2004 Sep;23(9):1241-4.
2. Macchia G, Deodato F, Cilla S, Torre G, Corrado G, Legge F, Gambacorta MA, Tagliaferri L, Mignogna S, Scambia G, Valentini V, Morganti AG, Ferrandina G. Volumetric intensity modulated arc therapy for stereotactic body radiosurgery in oligometastatic breast and gynecological cancers: feasibility and clinical results. *Oncol Rep*. 2014 Nov;32(5):2237-43. doi: 10.3892/or.2014.3412. Epub 2014 Aug 18

Malignant Pleural Effusion (8/13)

No further information

References :

1. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews 2004,
2. Bielsa S et al: Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung. 2011 Apr;189(2):151-5.
3. Ried M, Hofmann HS.: The treatment of pleural carcinosis with malignant pleural effusion. Dtsch Arztebl Int. 2013 May;110(18):313-8.
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Malignant Pleural Effusion - Local Therapy (9/13)

Further information and references:

Vote result of the AGO recommendation (complete slide without further changes): yes = 19/ no = 1

Statement: If expected survival is short, less invasive procedures should be considered (4 C ++)

1. Zamboni MM, da Silva CT Jr, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med. 2015 Mar 28;15:29. doi: 10.1186/s12890-015-0025-z.

Statements:

VATS and Talcum-pleurodesis (1b B ++)

Chemical pleurodesis

Talcum powder (1a B +)

Bleomycin, Doxycycline, Mitoxantrone (2b C +/-)

Povidone-iodine (20 ml of 10% solution) (1b B +)

Serial thoracocentesis (4 C +/-)

1. Hirata T et al: Efficacy of pleurodesis for malignant pleural effusions in breast cancer patients. Eur Respir J. 2011 Dec;38(6):1425-30
2. Mohsen TA et al: Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial. Eur J Cardiothorac Surg. 2011 Aug;40(2):282-6.
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4. Lombardi G, et al: Diagnosis and Treatment of Malignant Pleural Effusion: A Systematic Literature Review and New Approaches. Am J Clin Oncol. 2010 Aug;33(4):420-3.
5. Olden AM, Holloway R. Treatment of Malignant Pleural Effusion: PleuRx((R)) Catheter or Talc Pleurodesis? A Cost-Effectiveness Analysis. J Palliat Med. 2010 Jan;13(1):59-65.

6. Bazerbashi S, et al: Ambulatory Intercostal Drainage for the Management of Malignant Pleural Effusion: A Single Center Experience. *Ann Surg Oncol*. 2009 Dec;16(12):3482-7
7. Ried M, Hofmann HS.: The treatment of pleural carcinosis with malignant pleural effusion. *Dtsch Arztebl Int*. 2013 May;110(18):313-8.
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Statement: Continous pleural drainage (2a B +)

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.
3. Davies HE et al., Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012 Jun 13;307(22):2383-9. doi: 10.1001/jama.2012.5535.

Statement: Systemic treatment after pleurodesis (3b C +/-)

Statement: Local antibody therapy (i.e. Catumaxomab) (3b C -)

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.
2. Barni S, et al: A novel perspective for an orphan problem: old and new drugs for the medical management of malignant ascites.Crit Rev Oncol Hematol. 2011 Aug;79(2):144-53.
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.

References:

1. Cozzi S, et al: Management of neoplastic pericardial effusions. Tumori. 2010 Nov-Dec;96(6):926-9.
2. Kim SH, et al: Clinical characteristics of malignant pericardial effusion associated with recurrence and survival. Cancer Res Treat. 2010 Dec;42(4):210-6.
3. Kawase T, et al: Intense accumulation of Tc-99m MDP in pericardial metastasis from breast cancer. Clin Nucl Med. 2009 Mar;34(3):173-4.
4. Kil UH, et al: Prognosis of large, symptomatic pericardial effusion treated by echo-guided percutaneous pericardiocentesis. Clin Cardiol. 2008 Nov;31(11):531-7.
5. Dequanter D et al: Severe pericardial effusion in patients with concurrent malignancy: a retrospective analysis of prognostic factors influencing survival. Ann Surg Oncol. 2008 Nov;15(11):3268-71.
6. Toth I et al: Mediastinoscope-controlled parasternal fenestration of the pericardium: definitive surgical palliation of malignant pericardial effusion. J Cardiothorac Surg. 2012 Jun 19;7:56.
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8. Danielle El Haddad, MD,* Cezar Iliescu, MD,et al, Outcomes of Cancer Patients Undergoing Percutaneous Pericardiocentesis for Pericardial Effusion, 2015, J American Coll Cardiol, 66, NO. 10, 1119-1125

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.
5. Pahouja G, Wesolowski R, et al, Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin, *Cancer Treat Commun.* 2015 ; 3: 28–32.

Soft Tissue Metastasis - Local Therapy (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.
3. Tancioni F, et al: Multimodal approach to the management of metastatic epidural spinal cord compression (MESCC) due to solid tumors. Int J Radiat Oncol Biol Phys. 2010 Dec 1;78(5):1467-73. Epub 2010 Mar 16.
4. Rades, D et al.; Outcome after radiotherapy alone for metastatic spinal cord compression in patients with oligometastases. J. Clin. Oncol.,2007,25;50-6.
5. Gerszten PC, Monaco EA 3rd: Complete percutaneous treatment of vertebral body tumors causing spinal canal compromise using a transpedicular cavitation, cement augmentation, and radiosurgical technique. Neurosurg Focus. 2009 Dec;27(6):E9.
6. Souchon R, et al: DEGRO practice guidelines for palliative radiotherapy of metastatic breast cancer: bone metastases and metastatic spinal cord compression (MSCC). Strahlenther Onkol. 2009 Jul;185(7):417-24.
7. Abed R,et al: Soft-tissue metastases: their presentation and origin. J Bone Joint Surg Br. 2009 Aug;91(8):1083-5.
8. Kong JH, et al: Patterns of skin and soft tissue metastases from breast cancer according to subtypes: relationship between EGFR overexpression and skin manifestations. Oncology. 2011;81(1):55-62. Epub 2011 Sep 16.

9. Berlière M, Duhoux FP, Taburiaux L, Lacroix V, Galant C, Leconte I, Fellah L, Lecouvet F, Bouziane D, Piette P, Lengele B. The place of extensive surgery in locoregional recurrence and limited metastatic disease of breast cancer: preliminary results. *Biomed Res Int*. 2015;2015:782654. doi: 10.1155/2015/782654. Epub 2015 Mar 18.

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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CNS Metastases in Breast Cancer



CNS Metastases in Breast Cancer

- **Versions 2003–2015:**
**Bischoff / Diel / Friedrich / Gerber /
Huober / Lück / Maass / Müller / Nitz /
Jackisch / Jonat / Junkermann / Rody /
Schütz**

- **Version 2016:**
Loibl / Müller

In collaboration with:

P. Feyer und D. Rades (DEGRO)

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 specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de)**

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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Further
Information

References

**FORSCHEN
LEHREN
HEILEN**

Background OS-Score (Rades et al.)

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- Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed.
- This score was based on the four independent prognostic factors that were significantly associated with survival on multivariate analysis: age, performance status, extracranial metastases at the time of WBRT, and interval between tumor diagnosis and WBRT.
- The score for each prognostic factor was determined by dividing the 6-month survival rate (in %) by 10.
- The total score for each patient represented the sum of the scores for each prognostic factor.
- Total scores ranged from 9 to 18 points, and patients were divided into four groups.

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Further
Information

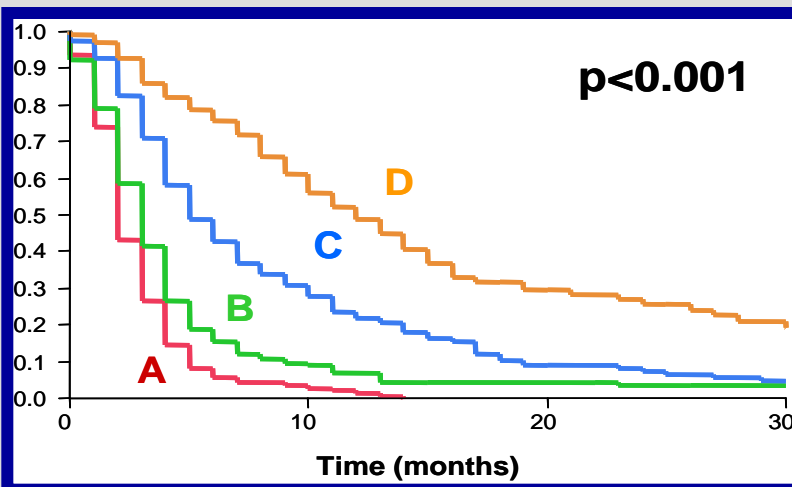
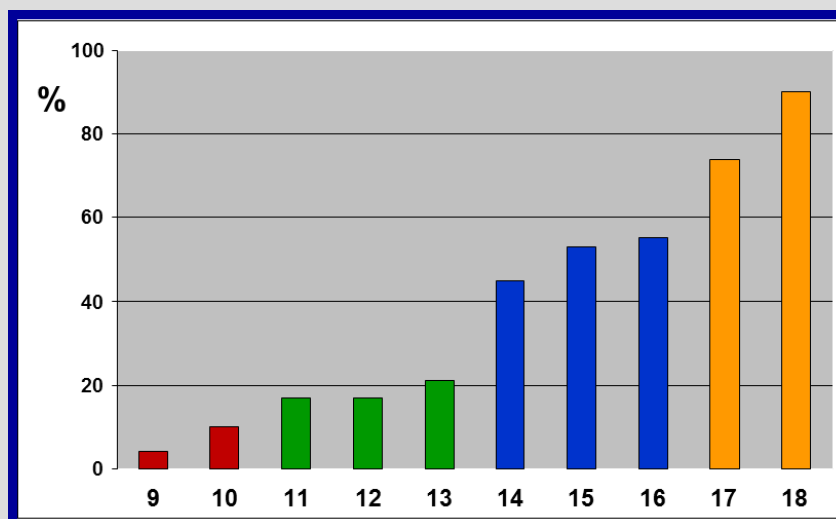
References

WBRT: Survival Score (N=1,085)

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	Überleben nach 6 Monaten (%)	Score
Alter		
≤ 60 Jahre	43	4
≥ 61 Jahre	25	3
Karnofsky-Index		
< 70	8	1
≥ 70	53	5
Extrakranielle Metastasen		
Nein	51	5
Ja	24	2
Intervall von Erstdiagnose bis GHRT		
≤ 8 Monate	32	3
> 8 Monate	36	4



**Score is already validated
(350 new patients).**

Rades et al., STO 2008
Dziggel et al., STO 2013

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References

FORSCHEN
LEHREN
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Single / Sole Brain Metastases

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Oxford/AGO

LoE / GR

Local therapy alone: SRS ($\leq 4\text{cm}$) o. FSRT o. Resection

2b B ++

WBRT + Boost (SRS, FSRT) o. Resection + WBRT

2a B ++

Resection + Irradiation of the tumor bed (without WBRT)

2b B +

WBRT alone*

2b B +

- WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.
- WBRT impairs neurocognitive function.
- In case of resection of the tumor the tumor bed has to be irradiated (either local RT or boost in case of WBRT).
- In general there is no advantage of surgical resection over RT.

* Patients with reduced general conditions and limited life expectancy

SRS = stereotactic radiosurgery (single session)
FSRT = fractionated stereotactic RT
WBRT = whole brain radiotherapy

2-3 (2-4) Brain Metastases (Oligo-)

Oxford/AGO

LoE / GR

Local therapy alone: SRS (≤ 4 cm) or FSRT

2b B ++

WBRT + Boost (SRS, FSRT)

2a B ++

WBRT alone *

2b B +

- **WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.**

- ***WBRT impaires neurocognitive function.**

- * **Patients with reduced general conditions and limited life expectancy**

SRS = stereotactic radiosurgery (single session

FSRT = fractionated stereotactic RT

WBRT = whole brain radiotherapy

NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases

Study design:

Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.

Conclusion:

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

Brown A, Asher AL, Ballman K, Farace E, Cerhan J, Anderson K, et al. J Clin Oncol 2015;33(Suppl):Abstract LBA 4.

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.

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 not allowing stereotactic radiotherapy

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery
- More than two lesions

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References

Multiple Brain Metastases >3 (4) Lesions

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➤ WBRT (supportive steroids*)	1a	A	++
➤ Hippocampus-sparing radiotherapy	2b	C	+/-
➤ Radiochemotherapy for cerebral disease control	3b	C	-
➤ Chemotherapy alone	3a	D	+/-
➤ Corticosteroids alone*	3a	B	+/-

***Adapted to symptoms**

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References

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HEILEN**

Systemic and Symptomatic Therapy of Brain Metastases

Oxford / AGO
LoE / GR

- | | | | |
|--|-----------|----------|------------|
| ➤ Continue anti-HER2-treatment | 2c | C | + |
| ➤ Lapatinib + Capecitabine as initial treatment (HER2 pos. disease) | 1b | B | +/- |
| ➤ Chemotherapy alone as primary treatment | 3 | D | - |
| ➤ Anticonvulsants only if symptoms of seizures | 3 | C | + |
| ➤ Glucocorticoids only when symptoms and / or mass effect | 3 | C | ++ |

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Further
Information

References

Leptomeningeal Carcinomatosis

Local Therapy

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Intrathecal or ventricular therapy

- MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)
- Liposomal cytarabine 50 mg, q 2w
- Thiothepa
- Steroids
- Trastuzumab (HER2 pos. disease)

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

Radiotherapy

- Focal (bulky disease)
- WBRT
- Neuroaxis (disseminated spinal lesions)

4	D	+
4	D	+
4	D	+/-

Due to bad prognosis consider best supportive care, especially in patients with poor performance status

CNS Metastases in Breast Cancer (2/15)

No further information

No references

CNS Metastases in Breast Cancer – Incidence (3/15)

No further information

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CNS Metastases in Breast Cancer (BC) Risk Factors (4/15)

Further information:

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an “unmasking” of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

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Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/15)

No further information

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Rades OS-Score (6-7/15)

No further information

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Singe / Solitary Brain Metastases (8/15)

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Brain Metastases 2-3 (2-4) lesions (9/15)

No further information

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See references Slide 8

NCCTG N0574 (Alliance): (10/15)

No further information

Reference:

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EORTC 22952- 26001 Study (11/15)

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No further information

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Systemic and Symptomatic Therapy of Brain Metastases (14/15)

No further information

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Leptomeningeal Carcinomatosis Local Therapy (15/15)

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

START

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Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship



Versions 2002–2015:

**Albert / Bauerfeind / Blohmer / Fersis /
Friedrich / Gerber / Göhring / Hanf / Janni /
Kümmel / von Minckwitz / Oberhoff / Scharl /
Schmidt / Schütz / Thomssen**



Version 2016: **Kümmel / Schmidt**

Further
Information

References

„Alternative“ Therapies

„Integrative Oncology“

„Unconventional methods“

CAM

Complementary + alternative medicine

UCT

Unconventional Thx

Complementary

*In addition to
scientifically
based medicine*

Alternative

*Instead of
scientifically
based medicine*

Unconventional

*Unproven outsider
methods*

General Considerations

Oxford AGO

LoE / GR

- | | | | |
|---|-----------|----------|-----------|
| ➤ Alternative methods (CAM)
instead of surgical treatment | 5 | D | -- |
| ➤ Alternative methods (CAM)
instead of systemic treatment | 2b | B | -- |
| ➤ <u>While on anti-cancer treatment: beware of drug interactions</u> | | | |

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Complementary Therapy

Pre- and Postoperative

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Preoperative:

- Hypnosis (reduces anxiety, pain, fatigue, nausea)

1b B +

Postoperative:

- Acupuncture (pain relief, anxiety, muscular discomfort)

2b B +/-

- Acupuncture (nausea, vomiting)

2b B +

- Massage Therapy (pain relief)

2b C +/-

- 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

**Oxford / AGO
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➤ **Mistletoe (*Viscum album*) in order to reduce side effects**

(influence on efficacy of anti-tumor therapy unknown)

1a B +/-

➤ **Thymic peptides** (lowered risk of severe infections)

(influence on efficacy of anti-tumor therapy unknown)

2a B +/-

➤ **Ginseng** (in order to reduce cancer related fatigue)

(note: ginseng inhibits cytochrome P enzymes
e.g. CYP 3A4)

2b C -

➤ **Ganoderma Lucidum** (may improve fatigue, note:

inhibits cytochrome P enzymes e.g. CYP 3A4)

2b C -

➤ **L-Carnitine** (given for prevention of toxicity, increased chemotherapy induced peripheral neuropathy)

1b B --

➤ **L-Carnitine does not improve cancer rel. Fatigue**

1b B --

➤ **Curcumin as an adjunct to reduce radio dermatitis**

1b B +/-

➤ **Ginger for chemotherapy induced nausea & vomiting**

1b C +/-

(consider interaction with anti-tumor drugs)

Complementary Treatment Impact on Toxicity II

	Oxford / LoE / GR		AGO
➤ Antioxidant supplements	1b	B	-
➤ High dose vitamine C	1b	C	-
➤ Vitamine E	2b	D	-
➤ Selenium for alleviating side effects of therapy	1b	B	-
➤ Co-Enzyme Q 10 (fatigue, QoL)	1b	B	-
➤ Proteolytic enzymes in order to reduce chemotherapy-induced toxicity	3b	B	-
➤ Chinese herbal medicine improves wound healing after mastectomy	1b	B	-*inf
➤ Oxygen and ozone therapy	5	D	- -

*inf: i.v.-infusion (in Germany not approved)

Additional Complementary Therapy

Side Effects Related to Cancer Treatments

e.g. Chemotherapy

Oxford LoE / GR AGO

➤ Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients

1b B -

- May offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life

➤ Homoeopathic medicines for adverse effects of cancer treatments

1b B +/-

- Topical calendula ($\geq 20\%$ Calendula amount) for prophylaxis of acute dermatitis during radiotherapy
- Traumeel S® mouthwash to treat chemotherapy-induced stomatitis

➤ Topical Silymarin for prophylaxis of acute dermatitis during radiotherapy

3a B +/-

➤ Acupuncture in order to improve on

- Chemotherapy-induced \geq nausea and vomiting
- Cognitive dysfunction
- Fatigue
- Pain
- Leucopenia (Moxibustion)
- Treatment of chemotherapy induced polyneuropathy

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

Complementary Treatment

Mind-Body Medicine I

Oxford / AGO
LoE / GR

MBSR (Mindfulness-Based Stress Reduction)

Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

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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Information

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Complementary Treatment

Mind-Body Medicine II

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➤ Yoga

- Improves sleep, quality of life, stress, anxiety, depression
- Improves fatigue

1b A +

1b A +

➤ Qi Gong

May improve quality of life, fatigue, mood

2a B +/-

➤ Tai Chi

Improves quality of life, physical performance

2a B +/-

- ### ➤ Hypnosis (in combination with cognitive training)
- Improves fatigue and muscle weakness under radiation therapy, also reduces distress

1b A +

Further
Information

References

Modifiable Lifestyle Factors

Prevention of Recurrence I

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LoE / GR

➤ Physical exercise

1a A ++

(Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)

➤ Smoking

1b A --

➤ Alcohol consumption (>6 g/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)

1a A ++

- Low fat diet (improves prognosis – DFS and OS) dietary counseling recommended

1a A +

- Avoid high-fat dairy products

2b C +

- Flaxseed/increased fibre intake

2a B +

- Adherence to general nutrition guidelines (e.g. DGE, WCRF)

2a B ++

- Dietary extremes (are associated with less favourable outcomes)

1b B - -

Complementary Treatment

Prevention of Recurrence III

Dietary Supplements – Herbal Therapies

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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

Oxford / AGO
LoE / GR

- **Acupuncture for cancer pain in adults** **1a B +/-**
- **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 - 01/2016
ASCO	2003 – 2015
SABCS	2003 – 2015
EBCC	2003 – 2015
Cochrane library:	summary Jan. 2016:

External advice:

The commission wants to thank the following external advisors for their contribution:

2010: Advice on nutritional facts by Prof. Dr. G. Stangl, Martin-Luther-University Halle Wittenberg, Germany

2011, 2013, 2015, 2016: Prof. Dr. G. Dobos and team,

Alfried Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen,
Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references

Alternative Therapies (3/14)

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.

No References

General Considerations (4/14)

No further information

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Complementary Therapy Pre- and Postoperative (5/14)

No further information

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Complementary Treatment - Prevention of Recurrence III (13/14)

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Complementary Treatment: Cancer Pain reduction (14/14)

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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Gynaecological Issues in Breast Cancer Patients

START

Gynaecologic Issues in Breast Cancer Patients

- **Version 2015:**
Loibl / Gerber
(with contribution from Hanf / Kümmel und Stickeler / Scharl)

- **Version 2016:**
Albert / Bauerfeind / Fersis / Thill

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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 (E3 0,03 mg)**
 - **Estradiol (E2) during AI therapy**

Oxford / AGO
LoE / GR

1b B -

2a B +/-

2b B +/-

1b A - -

4 D +/-

4 C -

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Alternative Medical Approaches to Reduce Menopausal Symptoms I

Oxford / AGO
LoE / GR

Medical approaches:

- | | | | |
|--|----|---|-----|
| ➤ Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients | | | |
| ➤ 1 st choice: venlafaxine | 1a | A | + |
| ➤ 2 nd choice: desvenlafaxine | 1b | A | +/- |
| ➤ 3 rd 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 | - |
| ➤ Melatonin (improvement in sleep quality) | 2b | C | + |

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CAM - Approaches to Reduce Menopausal Symptoms II

While anti-cancer treatment: Beware of drug interactions!

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➤ Soy-derived phytoestrogens – isoflavonoids			
Hot flush	1b	B	-
Sleep disturbance	1b	B	+/-
Topical vaginal application	1b	B	+/-
➤ Red Clover isoflavonoids			
Hot flush, sleep disturbance (might stimulate BC especially in endocrine responsive disease)	1b	B	+/-
➤ 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	B	-
➤ Black cohosh + St.John´s Worth	1b	B	+/-
➤ St. John´s Wort (in combination-therap)y (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)	1b	B	--
➤ Ginseng root (Panax ginseng or P. quinquefolius)	1b	B	-
➤ Bromelain + Papain + Selen + Lektin (for, AI induced joint symptoms)	3b	B	+

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General Approaches to Reduce Menopausal Symptoms III

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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	+/-

(no acupuncture in tumor bearing region, possibility of cell seeding)

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

Oxford / AGO
LoE / GR

➤ **Ovarian function protection**

➤ **CT + GnRHa**

(GnRHa application > 2 weeks prior to chemotherapy)

1a B +/-

Impairment of CT – effect cannot be excluded!

➤ **Fertility preservation counselling**

4 C +

➤ **Fertility preservation with
assisted reproduction therapy**

(further information www.fertiprotect.de)

4 C +

Ovarian Function Preservation – Comparison of Randomized Trials

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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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Author (year of publication)	Odds Ratio	95%CI	Treated Events	Controls Events
Li M (2008)	0.31	0.11-0.89	8/31	17/32
Badaway (2009)	0.06	0.02-0.20	4/39	26/39
Sverrisdottir 1 (2009)	0.19	0.04-1.06	14/22	18/20
Sverrisdottir 2 (2009)	2.03	0.31-13.27	27/29	20/23
Del Mastro (2011)	0.27	0.14-0.54	13/148	35/133
Gerber (2011)	0.56	0.19-1.62	9/30	13/30
Sun (2011)	0.38	0.06-2.30	3/11	5/10
Munster (2012)	1.09	0.22-5.52	4/26	3/21
Elgindy 1 (2013)	0.76	0.18-3.25	4/25	5/25
Elgindy 2 (2013)	1.0	0.25-4.00	5/25	5/25
Song (2013)	0.50	0.25-1.03	15/89	27/94
Karimi-zarchi (2014)	0.05	0.01-0.29	2/21	14/21
Li JW (2014)	0.44	0.04-4.35	1/54	3/73
Moore (2015)	0.30	0.10-0.87	5/66	15/69
Summary: Fixed effect	0.34	0.25-0.46	114/616	206/615
Summary: Random effect	0.36	0.23-0.57		

Lambertini M, Ceppi M, Poggio F, Peccator FA, Azim HA, Ugolini D, Pronzato P, Loibl S, Moore HCF, Partidge AH, Bruzzi P, Del Mastro. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol. 2015 Dec;26(12):2408-19.

Testing Ovarian Reserve

Oxford / AGO
LoE / GR

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

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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.

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Contraceptive Options for Women after Diagnosis of Breast Cancer

Oxford / AGO
LoE / GR

➤ Barrier methods	5	D	+
➤ Sterilization (tubal ligation / vasectomy)	5	D	+
➤ Non-hormonal intrauterine devices (IUDs)	3b	D	+
➤ Levonorgestrel-releasing IUDs	2b	C	-
➤ 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	-

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Emergency Contraception after Diagnosis of Breast Cancer

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LoE / GR**

➤ **Copper intrauterine device (Cu-IUD)**

5 D +

➤ **Levonorgestrel, Ulipristal**

5 D +

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Sexual Health

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|----------|
| ➤ Assessment of factors to sexual dysfunction | 5 | C | + |
| ➤ Use of patient-reported questionnaires | 4 | C | + |
| ➤ Vaginal dryness: | | | |
| Non-hormonal lubricants / moisturizers | 1b | B | + |
| ➤ Psychoeducational support, group therapy,
sexual counseling, marital counseling,
psychotherapy | 1b | B | + |

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Assessment of Sexual Health

➤ Sexual Complaints Screener (SCS) for women* German Translation

Screening-Check-Fragebogen: Overall Sexual Function

1. Are you satisfied with your sexual function?
yes, no; if no
2. How long have you been dissatisfied with your sexual function?
3. The problem(s) with your sexual function is: (mark one or more):
 1. Problem with little or no interest in sex
 2. Problem with decreased genital sensation (feeling)
 3. Problem with decreased vaginal lubrication (dryness)
 4. Problem reaching orgasm
 5. Problem with pain during sex
 6. Other
4. Which problem is most bothersome? (circle) 1, 2, 3, 4, 5, 6.
5. Would you like to talk about it with your doctor?

* Hatzichristou D, Rosen RC, Denogatis LR, Low WY, Sadovsky R, Symonds T.
Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348

Gynecological Issues in Breast Cancer Patients (2/15)

Further information:

Screened data bases:

- Pubmed 2009 –2015
- ASCO 2009 - 2015
- Cochrane 2009 - 2015
- Medline 2009 - 2015

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

No references

Hormonal (Replacement) Therapy of Estrogen Deficiency after Diagnosis of Breast Cancer (3/15)

No further information

References:

- 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
-
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-
- Tibolone:
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➤ Topical Vaginal Application:

Genitourinary syndrome of menopause (GSM) is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder (Portman DJ, 2014). For urogenital problems vaginal moisturizers, isoflavone or topical estrogens can be used (Ghazanfarpour M, 2015; Loibl S, 2011).

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7. Loibl S: Management of menopausal symptoms in breast cancer patients. *Maturitas*. 2012 Feb;68(2):148-54
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Alternative Medical Approaches to Reduce Menopausal Symptoms I (4/15)

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.(Haques R,2015) The use of paroxetine and fluoxetine should be avoided because they may reduce the efficacy of tamoxifen. Increased breast cancer mortality is associated with the use of paroxetine and tamoxifen (Chubak J, 2016; Kelly CM, 2010).

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)

Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes.(L'Espérance S, 2013; Kontos M, 2010)

References:

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SSRI:

Venlafaxine

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Fluoxetine

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Gabapentin

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Clonidine

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(D) MPA (depo-) (Medroxyprogesterone acetate)

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Vitamine E

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Melatonin

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CAM-Approaches to Reduce Menopausal Symptoms II (5/15)

Further information and references:

The majority of studies, regarding the efficacy of herbal treatments for menopausal symptoms – mostly hot flashes – have not been conducted in women with breast cancer and many are of short duration.(Roberts H, 2010) A recent systematic review retrieved 8 RCTs involving 798 breast cancer patients. Traditional herbal medicine combined with conventional therapy in the treatment of breast cancer has been efficacious in improving QOL and in decreasing the number of hot flashes per day (Kim W 2015). 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)

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Soy- and **red clover** derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated. Interaction may have breast cancer protecting and / or promoting effects.

Soy- derieved isoflavonoids

Five RCTs reported on the efficacy of soy for hot flashes, showing no significant reductions in hot flashes compared to placebo.

There is lack of evidence showing harm from use of soy with respect to risk of breast cancer or recurrence, based on long term observational data. Soy intake consistent with that of a traditional Japanese diet (2-3 servings daily, containing 25-50mg isoflavones) may be protective against breast cancer and recurrence. Human trials show that soy does not increase circulating estradiol or affect estrogen-responsive target tissues. Prospective data of soy use in women taking tamoxifen

does not indicate increased risk of recurrence. While there is no clear evidence of harm, better evidence confirming safety is required before use of high dose ($\geq 100\text{mg}$) isoflavones can be recommended for breast cancer patients (Fritz H, 2013).

Topical administration of soy-derived isoflavonoids

Topical isoflavones showed beneficial effects on dyspareunia, vaginal dryness and maturation value. Isoflavone vaginal gel was similar to the use of conjugated equine oestrogen cream (0.3 mg/day) was and superior to that of placebo gel (Ghazanfarpour M., 2015).

Red clover- derieved isoflavonoids

The systematic review and meta-analysis of 11 RCTs showed that red clover had a positive effect on alleviating hot flash in menopausal women.

Slight changes were found in FSH, LH, testosterone, and SHBG and more important a significant effect in estrogen status by red clover consumption. Red clover may increase the risk of estrogen-dependent cancers as estradiol showed a borderline increase in the red clover groups in comparison with control group based on three trials (Ghazanfarpour M, 2015).

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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).

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Taken together neither **Black cohosh** (*Cimicifuga racemosa*) (Leach MJ, 2012) nor **St John's Wort** (Caraci F, 2011) nor **Ginseng root** (Kim MS. 2013) showed a benefit regarding improvement of menopausal symptoms.

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2. 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.
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In a Phase III trial the fixed combination of Red Clover and St. John's Wort were significantly better in reducing menopausal symptoms than placebo.

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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.

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General Approaches to Reduce Menopausal Symptoms III (6/15)

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). The CBT and PE are cost-effective. Prescription is recommended by the authors (Mewes JC, 2015)

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)

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/15)

Further information:

Chemotherapy carries a risk of permanent ovarian failure. Ovarian protection is therefore discussed in patients who want to preserve fertility.

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

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Ovarian function protection CT+GNRH

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Ovarian Function Preservation Comparison of Randomized Trials (8/15)

Further information

This overview compares the different randomised trials comparing fertility preservation with GnRHanalogue without GnRHanalogue.

The ovarian failure rate at 2 years was statistically significant reduced from 22% without to 8% with GnRH treatment. Reassuringly the disease-free survival was not compromised by GnRH, in the contrary, the GnRH-group had a statistically significant improved DFS and (HR 0.49, $p=0.04$) as well as OFS (HR 0.43; $p=0.05$).

The number of pregnancies (22 vs. 12) and babies born (18 vs. 12) was also improved by goserelin.

The study by Munster et al. has not finished recruitment. Only 49 out of 124 planned pts were randomised. However, the results are in concordance with the ZORO study. Supporting the fact that the observed effect of LHRH is at its best small.

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Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure (9/15)

Further information

A recent meta-analysis of 12 randomized controlled trials investigated whether the use of LHRHa during chemotherapy in premenopausal breast cancer patients reduces treatment-related primature ovarian failure (POF) rate, increases pregnancy rate, and disease-free survival (DFS: median follow-up 4.1 years). Results were: „The use of LHRHa was associated with a significant reduced risk of primature ovarian failure (OR 0.36, 95% CI 0.23–0.57; $P < 0.001$), yet with significant heterogeneity ($I^2 = 47.1\%$, $P_{heterogeneity} = 0.026$). In eight studies reporting amenorrhea rates 1 year after chemotherapy completion, the addition of LHRHa reduced the risk of POF (OR 0.55, 95% CI 0.41–0.73, $P < 0.001$) without heterogeneity ($I^2 = 0.0\%$, $P_{heterogeneity} = 0.936$). In five studies reporting pregnancies, more patients treated with LHRHa achieved pregnancy (33 versus 19 women; OR 1.83, 95% CI 1.02–3.28, $P = 0.041$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.629$). In three studies reporting DFS, no difference was observed (HR 1.00, 95% CI 0.49–2.04, $P = 0.939$; $I^2 = 68.0\%$, $P_{heterogeneity} = 0.044$)“ The authors concluded: „Temporary ovarian suppression with LHRHa in young breast cancer patients is associated with a reduced risk of chemotherapy-induced primature ovarian failure and seems to increase the pregnancy rate, without an apparent negative consequence on prognosis.“ (Lampartini M et al. 2015)

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Testing Ovarian Reserve (10/15)

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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Assessment of Ovarian Reserve (11/15)

No further information

Reference:

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Contraceptive Options for Women after Diagnosis of Breast Cancer (12/15)

No further information

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Emergency Contraception after diagnosis of breast cancer (13/15)

No further information

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Sexual Health (14/15)

No further information

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Assessment of Sexual Health (15/15)

Further information:

Sexual Complaints Screener (SCS) for women
German Translation

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Diagnostik und Therapie von Patientinnen mit primärem und metastasierten Brustkrebs

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Guidelines Breast
Version 2016.1D

Optionen der primären Prävention: Veränderbare Lifestyle-Faktoren

◀ START

Prävention

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Guidelines Breast
Version 2016.1D

- **Version 2011:**
Gerber / Thomssen
- **Versionen 2012–15:**
Dall / Diel / Gerber/ Maass / Mundhenke
- **Version 2016:**
Dall / Maass

Nicht-modifizierbare Risikofaktoren für Brustkrebs

- **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)**
 - Bisher gibt es keine Evidenz für eine Korrelation zwischen Aluminium-enthaltenden Deodorants und Brustkrebsrisiko
 - Bisher gibt es keine Evidenz für die Glyphosat-Herbizid-Anwendung und eine Erhöhung des Brustkrebsrisikos

Hoher Anteil postmenopausaler Mamma-Ca durch Lifestyle-Faktoren

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Populations-spezifische Fraktionen (PAFs) von veränderbaren Risikofaktoren

Risikofaktoren: Adipositas, physische Inaktivität, Alkohol, Ballaststoff-arme Ernährung, Rauchen

Ergebnisse: retrospektive Kohortenstudie (Netherlands Cancer Registry)

2000: Subpopulationen von Frauen, inaktive, Alkoholkonsumenten, Raucher etc.
2010: Brustkrebsinzidenz im Vgl. zur Hintergrundinzidenz in diesen Subgruppen

25.7 % der postmenopausalen MaCa-Fälle in den Niederlanden
im Jahr 2010 sind verursacht durch ungesunde Lifestyle-Faktoren

8.8% bei Adipositas
6.6% bei Alkoholkonsum
5.5% bei körperlicher Inaktivität
3.2.% bei ballaststoffarmer Ernährung
4.6% bei Rauchern

Sekundäre Prävention, Lifestyle und TNBC Subgruppe

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TNBC Subgruppe:

n = 518 Pat., Populations-basierte prospektive Kohortenstudie, FU 9.1 J.

Faktor:	Rezidivrisiko
Phys. Aktivität	HR 0.58 (0.39-0.86)
BMI	keine Unterschiede

Bao et al., Epidemiology 2015, 26:909-16

Sekundäre Prävention, Lifestyle und ER-positive Subgruppe

ER-positive Subgruppe:

n = 6295 Pat., prospektive Pool-Studie, 5 J. nach Diagnose

keine Gewichtsänd.	HR 1.00
≥ 10% Zunahme	HR 1.24 (1.00-1.53)
BMI 30-34.99	HR 1.40 (1.05-1.86)
BMI >35	HR 1.41 (1.02-1.62)
kein Alkohol	HR 1.00
täglich Alkohol	HR 1.28 (1.091-1.62)
phys. Aktivität	
kein Sport	HR 1.00
< 17.4 MET-h/wk	HR 0.81 (0.71-0.93)
≥ 17.4 MET-h/wk	HR 0.71 (0.61-0.82)

Nechuta et al., Int J Cancer, DOI 10.1002 (Epub ahead of print)

Präventiver Einfluss durch das Reproduktionsverhalten

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

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LoE / GR

2b B

2b B

2b B

3a B

Prävention durch Änderung von Lifestyle-Faktoren: Gewicht / Glucosestoffwechsel

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

- Prämenopausal
- Postmenopausal

Oxford / AGO
LoE / GR

2a B ++

3a B ++

2a B ++

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

(Reduktion der Brustkrebsinzidenz und -mortalität)

2b B ++

Prävention durch Änderung von Lifestyle-Faktoren: Ernährung

Oxford / AGO
LoE / GR

- | | | | |
|---|-----------|----------|-------------|
| ➤ Bevorzugung einer gesunden Diät | 2b | B | + |
| ➤ 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 Lifestyle-Faktoren: Alkohol

**Oxford / AGO
LoE / GR**

- **Reduktion des Alkoholkonsums
vermindert Brustkrebsrisiko**

2b B

Insbesondere für

- **ER+/PgR+ Tumoren**
- **Invasiv lobuläre Tumoren**

2b B

2b B

Prävention durch Änderung von Lifestyle-Faktoren: Rauchen

Oxford / AGO
LoE / GR

- **Frauen, die nie geraucht haben, haben ein verringertes Lebenszeitrisiko für einen Brustkrebs (~ 15-24% Reduktion)** **2a B ++**
- **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 Lifestyle-Faktoren: Körperliche Aktivität

Oxford / AGO
LoE / GR

➤ Körperliche Aktivität

2a⁽⁻⁾ B ++

**Metabolisches Equivalent zu 3–5 Std.
Spaziergänge pro Woche mit
moderater Schrittgeschwindigkeit**

Prävention durch Lifestyle-Faktoren: 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 in der Postmenopause

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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

Hormonsubstitution bei postmenopausalen Patienten

	N	MC-RR(95%CI)	Weitere Aussagen
CLEAR-study (NSW)	1236 BC cases	2.09 (1,57-2.78)	bei laufender Einnahme
		1.03 (0.82-1.28)	frühere Einnahme
		2.62 (1.56-4.38)	E/P Kombination
		1.80 (1.21-2.68)	E Monosubstitution
Case-Control-Study, retrospect. Australia			

Prävention durch Änderung von Lifestyle-Faktoren: 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(-)

Diagnostik und Therapie von Patientinnen mit primärem und metastasierten Brustkrebs

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Brustkrebsrisiko und Prävention

Brustkrebsrisiko und Prävention

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- **Versionen 2003–2015:**
**Schmutzler with Albert / Blohmer / Fehm /
Kiechle / Maass / Mundhenke / Rody /
Schmidt / Thomssen**
- **Version 2016:**
Schmutzler / Stickeler

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 ca. 25.000 Familien, getestet bis 2015; bei Vorliegen eines dieser EK liegt die Wahrscheinlichkeit für den Nachweis einer Mutation bei $\geq 10\%$**

Empfohlene Screening Checkliste *

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8350379533 Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs (Mamma-Ca incl. DCIS)

Name der Patientin: _____ Geburtsdatum: ____/____/____

A. Patientin oder Patient und deren Eltern/Geschwister/Kinder	ggf. Anzahl (wie angegeben)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei der Patientin vor dem 36. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei der Patientin vor dem 51. LJ	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei der Patientin, das erste vor dem 51. LJ	<input type="checkbox"/> 1	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin nach dem 50. LJ	<input type="checkbox"/> 1	1	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei der Patientin	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einem Patienten (incl.)	<input type="checkbox"/> 1	2	<input type="checkbox"/>
eines Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Müttern/Nichten nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei Brüdern/Söhnen/Vätern/Neffen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms/primären Peritonealkarzinose bei Schwestern/Töchtern/Müttern/Nichten	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe Patientin und deren Eltern/Geschwister/Kinder	A <input type="text"/>		
B. Weitere mütterliche Linie	Anzahl (wie angegeben)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere mütterliche Linie	B <input type="text"/>		
C. weitere väterliche Linie	Anzahl (wie angegeben)	Gewicht- ung	Er- gebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	3	<input type="checkbox"/>
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	1	<input type="checkbox"/>
eines Mamma-Karzinoms bei einem angehörigen Mann	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
eines Ovarial-/Tuberkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3	2	<input type="checkbox"/>
Summe weitere väterliche Linie	C <input type="text"/>		
D. Der höhere Wert aus B und C	D <input type="text"/>		
E. Summe aus A und D = Risiko-Score	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> >7 A+D <input type="text"/>		

Version: 06. Januar 2016 (© Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs)

Formular design: BKKL, Hübner, Version 2.1

SchutzlarK20AuftragK20164.pdf

*online tool provided by the Ärztekammer Westfalen-Lippe in cooperation with the GC-HBOC based on the inclusion criteria of the GC-HBOC, www.aekwl.de/fileadmin/qualitaetssicherung/Zertifizierungsstelle/FB-erbliche_Belastung_V2016-01-06.pdf

BRCA1/2 Analyse in Patienten mit TNBC (unabhängig von der Familienanamnese)

BRCA1/2 Untersuchung bei 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**

Mutationsprävalenzen beim TNBC

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	<35 y	35-39 y	40-49 y	50-59 y	>=60 y	Total
No BC, no OC	18/91 (23%)	23/149 (15.4%)	18/209 (8.6%)	18/241 (7.5%)	6/279 (1.4%)	83/969 (8.5%)
1 BC, no OC	7/48 (14.6%)	7/50 (14%)	14/103 (13.6%)	5/80 (6.3%)	4/79 (5.1%)	37/360 (10.3%)
>=2 BC, no OC	6/12 (50%)	6/16 (37.5%)	8/38 (21%)	2/28 (7.1%)	1/23 (0%)	23/117 (19.7%)
>= 1 OC	3/5 (60%)	8/15 (53.3%)	7/18 (38.9%)	10/17 (58.8%)	1/7 (14.3%)	29/62 (46.8%)
Total	34/156 (21.8%)	44/230 (19.1%)	47/368 (12.8%)	35/366 (9.6%)	12/388 (3.1%)	173/1508 (11%)

www.ago-online.de

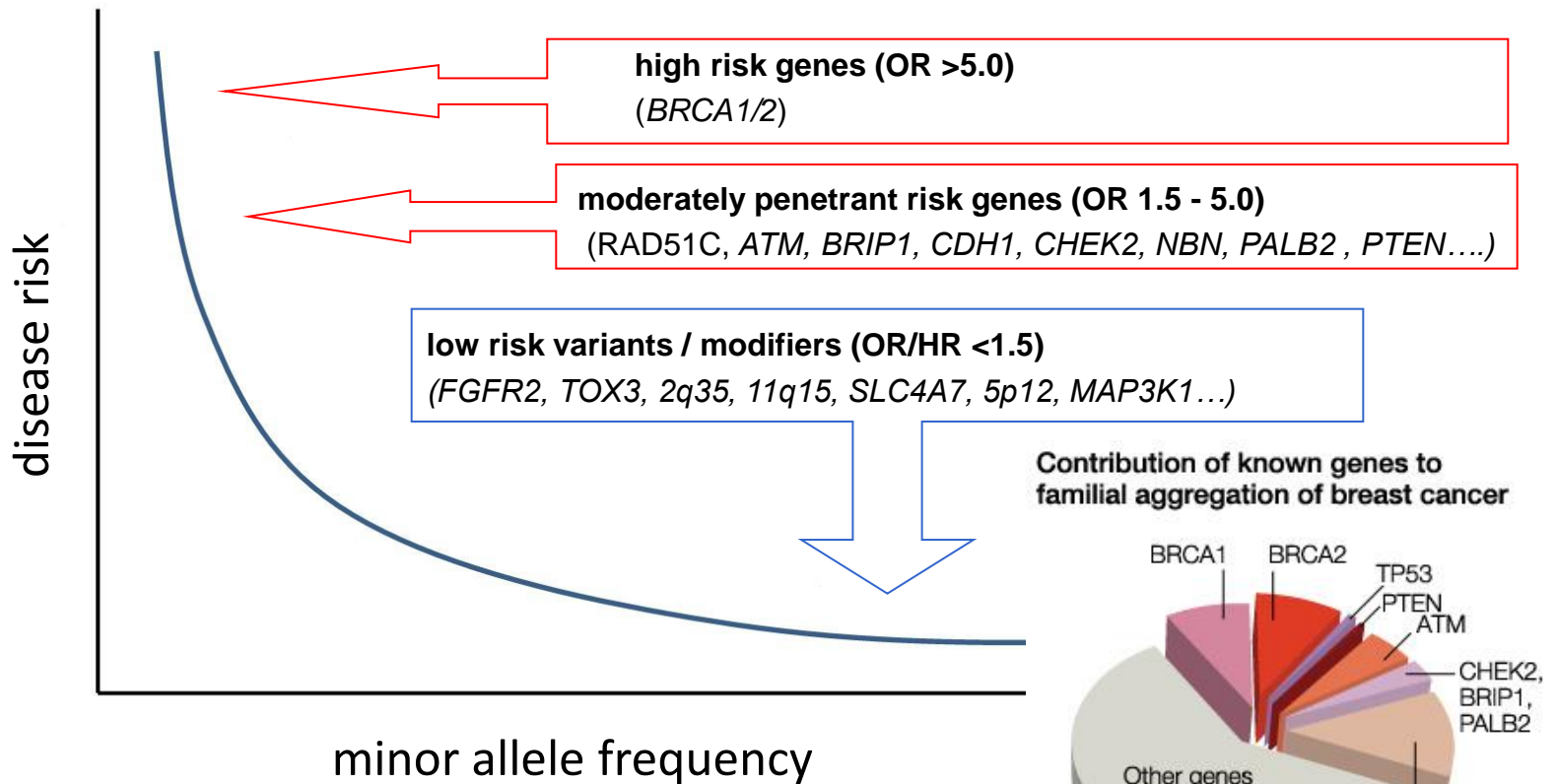
FORSCHEN
LEHREN
HEILEN

Couch et al. JCO DOI 10.1200/JCO.2014.57.1414

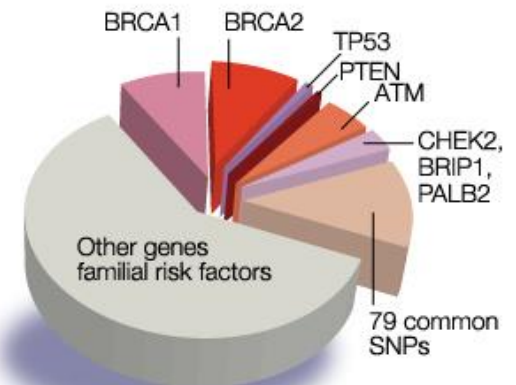
Stand der Forschung: Oligogenetischer Erbgang und genetische Heterogenität

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Contribution of known genes to
familial aggregation of breast cancer



Nicht BRCA-assoziierte erbliche Krebs syndrome mit erhöhtem Brustkrebsrisiko

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 %
Ataxia telangiectasia (AT-Syndrome)	ATM	20-40 % ⁶
Franconi Anämie	RAD51C / D PALB2	Ovary: ~ 10 % ^{7,8} > 30 % ⁹
Nijmegen-Breakage Syndrome	NBN	20-30 % ^{10,11} for slavic founder mutation 657del5

Empfehlung: genetische Beratung: GCP

Nicht validierte Brustkrebs-Genpanels

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)

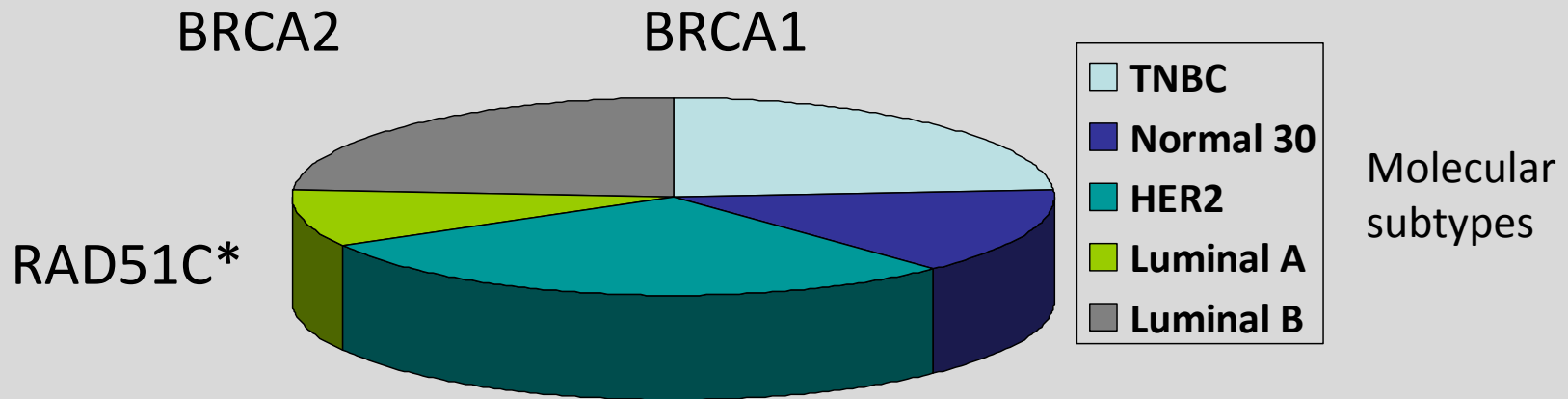
Strategie:

➤ 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 (≤ 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 Klassifikation der Sequenzvarianten sollte entsprechend der IARC Klassifikation erfolgen
- Die VUS Klassifikation und klinische Entscheidungsfindung sind bisher nicht standardisiert

Klassifikation der Varianten nach IARC (Plon et al., Human Mutation, 2008)

Proposed Classification System for Sequence Variants Identified
by Genetic Testing

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

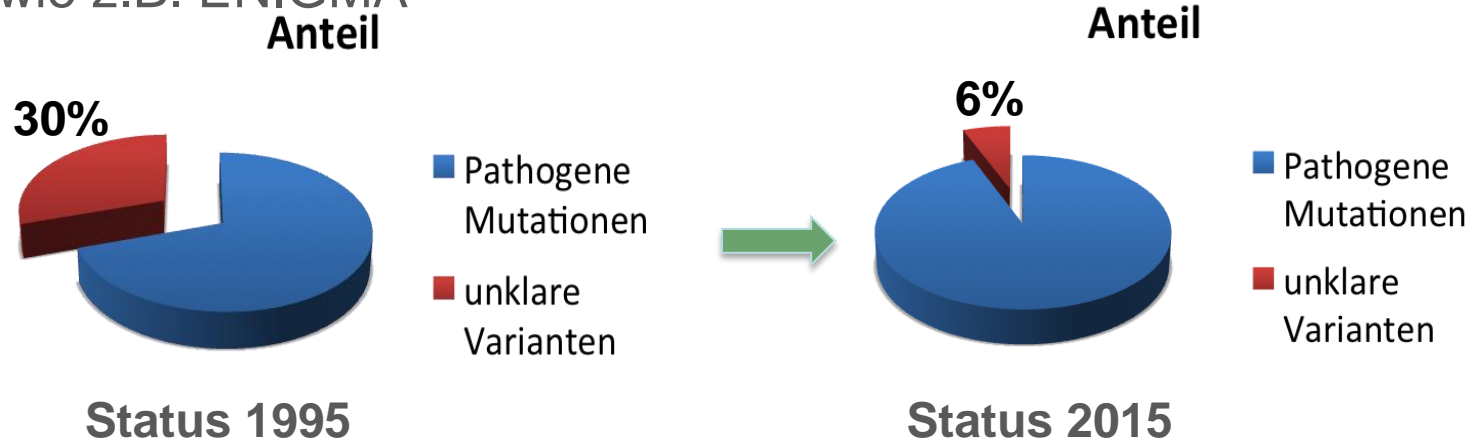
Nur Klasse 4 und 5 Varianten gelten als klinisch relevant

Klassifikation der IARC Klasse 3 Varianten

erfordert weitere Informationen und Analysen, z.B.

- Ko-aufretens Daten von großen Datenbanken
- Segregationsanalysen
- Funktionsanalysen etc.

Sollten zusammengeführt werden in großen Studiengruppen wie z.B. ENIGMA



Verbesserung der IARC Klasse 3 Klassifikation in der Deutschen Population durch das Dt. Konsortium

Voraussetzungen für die Einführung neuer prädiktiver oder diagnostischer genetischer Marker

- 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

Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health
<http://www.bmg.bund.de/themen/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/querschnittsthema-risiko-adaptierte-krebsfrueherkennung.html>

Gegenwärtige klin. Bedeutung weiterer Risikogene

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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	++

Nicht-direktive Beratung vor der Durchführung präventiver Maßnahmen

Oxford / AGO
LoE / GR

GCP C ++

- 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

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Definition von Frauen mit moderatem und hohem Erkrankungsrisiko

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➤ Mutation in den Genen BRCA1, BRCA2

1a A ++

➤ Heterozygotenrisiko $\geq 20\%$ oder
verbleibendes Lebenszeitrisiko $\geq 30\%$
(nach standardisiertem
Prädiktionsmodell)

2b B +

➤ Überlebende nach kindlichen Tumoren
mit therapeutischer Radiatio der
Brustwand (z.B. M. Hodgkin)

2a B ++

Multimodales Früherkennungsprogramm bei Frauen mit BRCA1/2 Mutation*

Oxford / AGO
LOE / GR

➤ Multimodales intensiviertes lebenslanges Früherkennungsprogramm

➤ Zum Nachweis früher Tumorstadien

2a B ++

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

➤ Zur Mortalitätsreduktion

3 B +

*Das Früherkennungsprogramm sollte an den Zentren für Familiären Brust- und Eierstockkrebs (GC-HBOC) oder kooperierenden Zentren durchgeführt werden.

MRI Breast Screening in High-risk Women

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MRI breast screening in high-risk women: cancer detection and survival analysis. Evans DG, Kesavan N, Lim Y, Gadde S, Hurley E, Massat NJ, Maxwell AJ, Ingham S, Eeles R, Leach MO, MARIBS Group, Howell A, Duffy SW. Breast Cancer Res Treat. 2014 Jun;145(3):663-72. doi: 10.1007/s10549-014-2931-9. Epub 2014 Apr 1.

**See Table 4: Five- and 10-year overall survival in BRCA women and
Figure 1: overall survival in BRCA women**

Multimodales Nachsorgeprogramm bei Frauen mit BRCA1/2 Mutation nach primärer Erkrankung*

**Oxford / AGO
LOE / GR**

➤ Multimodales intensiviertes lebenslanges Früherkennungsprogramm

➤ Zum Nachweis früher Tumorstadien

2a B ++

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

➤ Zur Mortalitätsreduktion

4 C +

***Das Früherkennungsprogramm sollte an den Zentren für Familiären Brust- und Eierstockkrebs (GC-HBOC) oder kooperierenden Zentren durchgeführt werden.**

Früherkennungsprogramm für Männer mit BRCA Mutationen*

BRCA1 Mutationsträger haben ein nahezu normales Erkrankungsrisiko für Brustkrebs und ein 1.8-4.5-faches Risiko für ein Prostatakarzinom $\leq 65y$.

BRCA2 Mutationsträger haben ein 5-7% Lebenszeitrisiko für Brustkrebs und ein 2,5- bis 8,6-faches Risiko für ein Prostatakarzinom $\leq 65y$.

Aktuell kein spezifisches Früherkennungsprogramm

**Oxford / AGO
LoE / GR**

➤ **Für Brustkrebsprävention:**

Selbstuntersuchung und Watchful waiting

5 D +

➤ **Für Prostatakarzinomprävention:**

Studienbeteiligung möglich

3b C +

***Das Früherkennungsprogramm sollte an den Zentren für Familiären Brust- und Eierstockkrebs (GC-HBOC) oder kooperierenden Zentren durchgeführt werden.**

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 GC-HBOC oder kooperierende Zentren zur Evaluation der Früherkennung und des Follow-up

Chirurgische Prävention

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- **Eine sekundär prophylaktische unilaterale oder bilaterale Mastektomie ist ohne das Vorliegen von genetischen Risikofaktoren nicht indiziert**

2a

B +*

Chirurgische Prävention bei gesunden BRCA1/2 Mutationsträgerinnen

Oxford / AGO
LOE / GR

- | | |
|---|------------------------------|
| <p>➤ Prophylaktische bilaterale Salpingo-Oophorektomie (PBSO)</p> <ul style="list-style-type: none"> - Reduziert die Brustkrebsinzidenz und -mortalität - Reduziert die Eierstockkrebsinzidenz und -mortalität - Reduziert die Gesamtmortalität | <p>2a B ++*</p> |
| <p>➤ Prophylaktische bilaterale Mastektomie (PBM)</p> <ul style="list-style-type: none"> - Reduziert die Brustkrebsinzidenz und -mortalität | <p>2a B +*</p> |

Die PBSO wird nach Abschluss der Familienplanung empfohlen
Die Ablate nach PBM zeigen eine erhöhte Rate an prämaligen Läsionen

*** Studienteilnahme empfohlen**

Risiko- reduzierende Interventionen bei erkrankten BRCA1/2 Mutation Trägerinnen

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- **Bilaterale Salpingo-Oophorectomy (RR-BSO)**
reduziert OvCa Inzidenz und Mortalität
reduziert Brustkrebsmortalität
reduziert Gesamtmortalität
(gegensätzlich Ergebnisse bezgl. kontralateraler Brustkrebsinzidenz)
- **Kontralaterale Mastektomie (PBM)**
reduziert kontralaterale Brustkrebsinzidenz
- **Tamoxifen (reduziert kontralat. BrCa inzidenz)**
- **Indikationsstellung für PBM sollte Alter,**
- **Ersterkrankungsalter und betroffenes Gen berücksichtigen**

2b B +*

2b B +/-*

2b B +/-*

2a B ++*

+ Gesamtprognose muss berücksichtigt werden

*Studienteilnahme empfohlen

Improved Overall Survival After Contralateral Risk-reducing Mastectomy in BRCA1/2 Mutation Carriers

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Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. Heemskerk-Gerritsen BA1, Rookus MA, Aalfs CM, Ausems MG, Collée JM, Jansen L, Kets CM, Keymeulen KB, Koppert LB, Meijers-Heijboer HE, Mooij TM, Tollenaar RA, Vasen HF; HEBON, Hooning MJ, Seynaeve C.

Int J Cancer. 2015 Feb 1;136(3):668-77. doi: 10.1002/ijc.29032. Epub 2014 Jul 8.

See table 3: Efficacy of contralateral risk-reducing mastectomy on overall survival

We conclude that CRRM is associated with improved overall survival in BRCA1/2 mutation carriers with a history of PBC. Further research is warranted to develop a model based on age at diagnosis and tumour and treatment characteristics that can predict survival benefit for specific subgroups of patients, aiming at further personalized counselling and improved decision making.

Therapie des BRCA1/2-assoziierten Mammakarzinoms⁺

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**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 metastasiertem
Mammakarzinom** **2b^a B +**
 - **PARP-Inhibitoren bei metastasiertem Mammakarzinom** **2a B +/-***
- + Gesamtprognose muss berücksichtigt werden**

*** Studienteilnahme empfohlen**

BRCA Mutations, Therapy Response and Prognosis in the Neoadjuvant GeparQuinto

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Tanja Fehm, Jens Huober, Cornelia Liedtke, Volkmar Müller,
Valentina Nekljudova, Karsten E Weber, Brigitte Rack,
Matthias Rübner, Liewei Wang, James N Ingle,
Richard M Weinshilboum, Gunter von Minckwitz and Fergus
Couch**

**for the
GBG/AGO-B study groups**

Early Survival Analysis of the Randomized Phase II Trial Investigating the Addition of Carboplatin to Neoadjuvant Therapy for Triple-negative and HER2-positive Early Breast Cancer (GeparSixto)



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Gunter von Minckwitz, Sibylle Loibl, Andreas Schneeweiss, Christoph Salat, Eric Hahnen, Mahdi Rezai, Dirk Michael Zahm, Peter Klare, Jens Uwe Blohmer, Hans Tesch, Fariba Khandan, Peter Fasching, Christian Jackisch, Rita Schmutzler, Valentina Nekljudova, Michael Untch

**for the
GBG/AGO-B study groups**

www.ago-online.de

**FORSCHEN
LEHREN
HEILEN**

Medikamentöse Prävention für Frauen mit erhöhtem Risiko

Oxford / AGO
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➤ **Tamoxifen für Frauen > 35 Jahre**
Reduktion des invasiven MaCa, DCIS und LN

1a A +*

➤ **Raloxifen für postmenopausale Frauen**
Reduktion des invasiven MaCa

1b A +*

➤ **Aromatasehemmer für postmenopausale Frauen**

1b A +[#]

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

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

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

Risikoreduktion für das ipsi- und kontralaterale Mammakarzinom

Frauen nach Brustkrebs haben ein erhöhtes Risiko für ein kontralaterales Zweitkarzinom

➤ **Tamoxifen***

➤ **Aromatasehemmer***

➤ **GnRHa + Tamoxifen***

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1a A +

1a A +

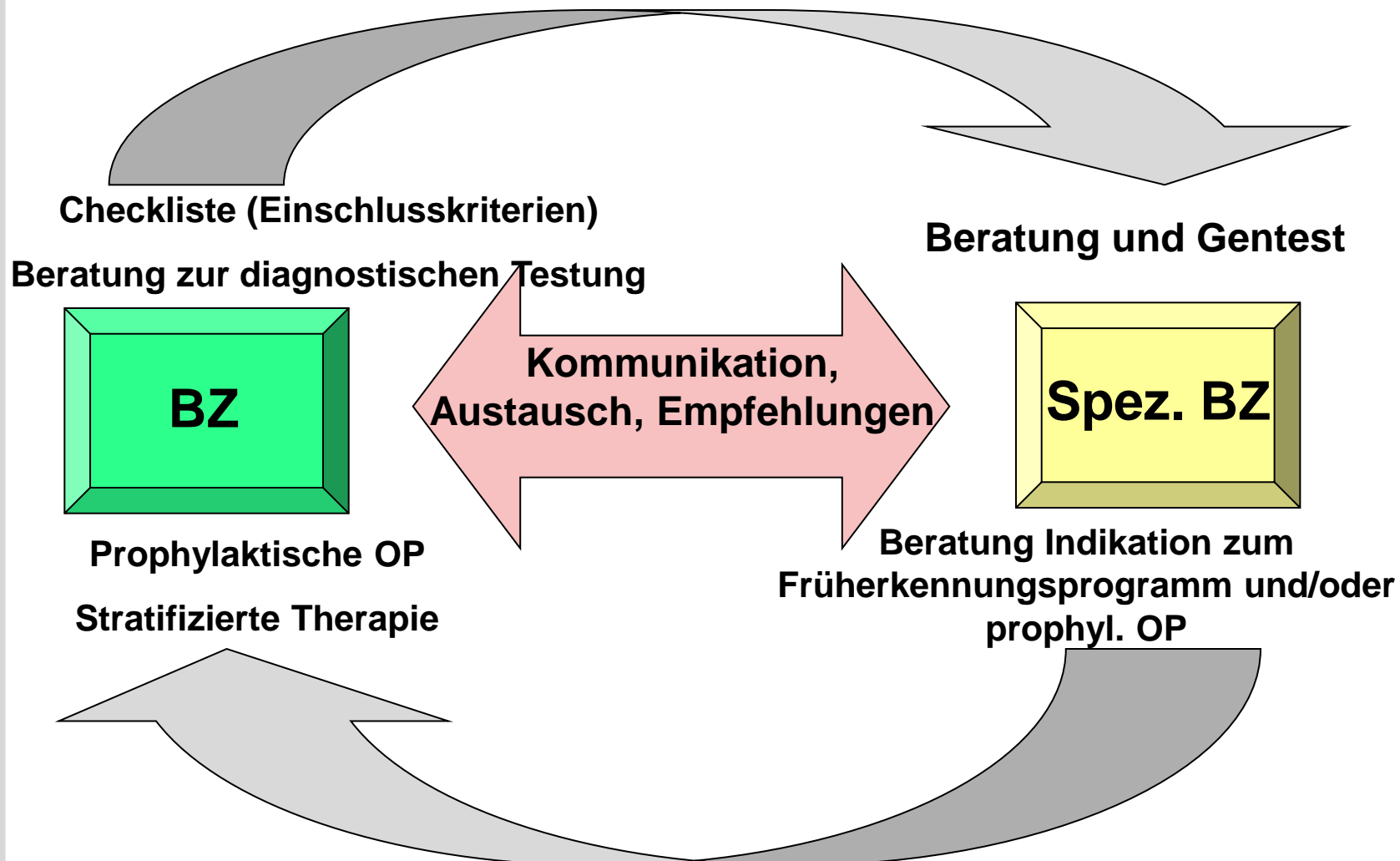
1b B +

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

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

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* Transsektoraler Vertrag zur integrierten Versorgung nach SGB § 140a seit 2015

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Früherkennung und Diagnostik

Früherkennung und Diagnostik

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- **Versionen 2005–2015:**
**Albert / Blohmer / Fersis / Junkermann /
Maass / Scharl / Schreer**
- **Version 2016:**
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)

Brustkrebs Mortalitätsreduktion

Meta-Analyses

RR (95%CI)

Case-Control Studies

Broeders et al	Screening Mx	0.46 (0.4 – 0.54)
	Corr. for self selection	0.52 (0.42-0.65)
	Invited for screening	0.69 (0.57-0.83)

Incidence-based Mortality Studies

Broeders et al	Screening Mx	0.62 (0.56-0.69)
	Invited to screening	0.75 (0.69-0.81)

Randomized Clinical Trials

Gotsche and Jorgenson	Screening Mx	0.81 (0.74-0.87)
-----------------------	--------------	------------------

Brustkrebs Mortalitätsreduktion

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Age Group (yrs)	NNS	
	Mortality Reduction 20%	40%
40 - 49	1770	753
50 - 59	1087	462
60 - 69	835	355

4 systematic reviews of 8 RCTs,
1 systematic review of 7 cohort studies and metaanalysis of case-control studies

Oeffinger KC et al JAMA 2015;314

Breast Cancer Screening

ACS Guideline Update 2015

American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age.

The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

Recommendations

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)

1a. Women aged 45 to 54 years should be screened annually. (*Qualified Recommendation*)

1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. (*Qualified Recommendation*)

1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (*Qualified Recommendation*)

2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. (*Qualified Recommendation*)

3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. (*Qualified Recommendation*)

^aA strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.¹

Breast-Cancer Screening- Viewpoint of the IARC Working Group

Method	Strength of Evidence
Reduces breast-cancer mortality in women 50-69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70-74 yr of age	Sufficient
Reduces breast-cancer mortality in women 40-44 yr of age	Limited
Reduces breast-cancer mortality in women 45-49 yr of age	Limited
Detects breast cancer that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50-74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50-69 yr of age who are invited to attend organized mammographic screening programs	Sufficient

Mammographie-Screening

Frauen 40–49 Jahre

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

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

Früherkennung Sonographie

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- **Screening-Mammasonographie**
 - **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

Oxford / AGO
LOE / GR

➤ Klinische Untersuchung	3b	B	++
➤ Mammographie	1b	A	++
➤ Tomosynthese (vs Spotkompression)	2b	B	+
➤ Sonographie	2b	B	++
➤ Elastographie (Shear wave)	2a	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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	Oxford / AGO LOE / GR		
➤ Klinische Untersuchung	5	D	++
➤ Mammographie	2b	B	++
➤ Mammographie + Tomosynthese + Sonographie added MRI	3b 3b	B B	+ -
➤ Sonographie Axillasono.+ FNA/CNB	2b 2b	B 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?)**

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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	-

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.“

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Pathologie



Pathologie

- **Versionen 2004–2015:**
**Costa / Fehm / Friedrichs / Huober /
Kreipe / Lück / Sinn / Thomssen**
- **Version 2016:**
Blohmer / Kreipe

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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)**
- **Einhaltung einer minimalen Fixationszeit von 6 Stunden zur Gewährleistung einer optimalen Antigenerhaltung**
- **Optimale Fixationszeit bei Stanzbiopsien: 6 - 72 h**
- **Optimale Fixationszeit bei Resektaten: 12 - 72 h**
- **Verwendung neutral gepufferter Formalinlösung**

5 D ++

5 D ++

5 D ++

5 D ++

5 D ++

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

Oxford / AGO
LoE / GR

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

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FORSCHEN
LEHREN
HEILEN

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

Oxford
LoE / GR

AGO

- **Anwendung des Nottingham-Grading (Elston & Ellis 1991) für alle Typen des invasiven Mammakarzinoms**
- **Bei sehr wenig Tumorgewebe rein nukleäres Grading oder Heranziehung zusätzlicher Kriterien wie Ki-67 Proliferationsfraktion**
- **Grading des DCIS gemäß WHO-Klassifikation des Mammakarzinoms (4. Aufl., 2012)**
- **Wiedergabe des Tumorgrading zumindest auch numerisch (z.B. G3)**

5 D ++

5 D ++

5 D ++

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-Klassification

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
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AGO

5 D +/-

- **Identifikation von Tumoren mit prädominantem lymphozytärem Infiltrat (> 50%) im Tumorstroma (n. Salgado et al.*)**

Nur das intratumorale Infiltrat im Stroma und nicht 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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➤ 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	1a	A	++
➤ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 1\%$; niedrig positiv bei $\geq 1\%$ bis 9%)	1a	A	++
➤ Angabe der Färbeintensität (0 - 3)	4	D	+
➤ Allred Score (0–8), Remmele Score (0 - 12)	4	D	+
➤ Reevaluation am Exzidat, wenn unklarer Befund an der Stanze oder triple-negativer Tumor	5	D	+

Zusatzuntersuchungen: Bestimmung des PgR mittels IHC

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	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

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

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 duktales or lobuläres Karzinom, ER und PgR positiv, tubulär, muzinös, kribriform, 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

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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 duktal 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 $15\% \pm 5\%$**
- **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

◀◀ START

Prognostische und prädiktive Faktoren

- **Versionen 2002–2015:**
**Costa / Fersis / Friedrichs / Gerber /
Göhring / Harbeck / Janni / Liedtke / Loibl /
Mundhenke / Nitz / Rody / Schaller /
Schmidt / Schmutzler / Schneeweiss /
Simon / Solomayer / Thomssen**
- **Version 2016:**
Witzel / Nitz

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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 that 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

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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

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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
➤ Tumorgröße	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: concordance central vs local is high (97%; Plan B, SABCS 2014)**
- **Grading: concordance central vs local is 68 % (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)**
- **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%, in central pathology review (Ann Oncol 2012)**
- **Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)**

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/Ki-67 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	+

[§] 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	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
Prospective- retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%)	ABCSG 6 (19%) ABCSG 8 (36%) GEICAM-9906 (45%) ATAC (10%)	MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%)
Prospective evidence	MINDACT (completed)	TAILOR _x (N0, low-risk, RS<11) PlanB (N0, high- risk/N+)	-	-

\$ 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	A	+/-
➤ Therapieentscheidungen basierte auf CTC-Phänotypen	III	C	-
➤ Multigene assays			
➤ (Oncotype DX®) (N0-/+, HR+ HER2-, 5 Jahre)	I	A	+
➤ (EndoPredict®, Prosigna®) (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 Chemotherapie

Therapieprädiktion II

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Faktor	LoE ₂₀₀₉	CTS	GR	AGO
➤ Multigensignatur (Mammaprint, Endopredict Oncotype Dx, Prosigna ^{\$})	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumor infiltrating Lymphocytes*	I	B	B	+
➤ PIK3CA mutation	II	B	B	+/-

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

* Definiert als dichte lymphozytäre Infiltration des inneren peritumoralen Stromas außerhalb der Invasionsfront (Stroma besteht mit > 50% aus Lymphozyten)

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 \$	+/-

\$ Validierte klinische Daten nur verfügbar für diesen Assay.

Prognosefaktoren – Metastasiertes Mammakarzinom

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Faktor	LoE ₂₀₀₉	CTS	AGO
➤ Zirkulierende Tumorzellen (CTC im Blut, Cell Search®)			
➤ Prognose	I	A	+
➤ Frühes Therapieansprechen (3 Wo.)	I	B	+
➤ Therapieentscheidungen basiert auf CTC-Anzahl oder CTC-Phänotypen	I	A	-*

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Läsionen mit unsicherem biologischen Potenzial (B3)

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

◀◀ START

Läsionen mit unklarem biologischen Potenzial (B3)

- **Versionen 2005–2015:**
**Albert / Audretsch / Brunnert / Fersis /
Friedrich / Gerber / Kreipe / Nitz / Rody /
Schreer / Sinn / Thomssen**
- **Version 2016:**
Friederichs / Sinn

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 duktale Hyperplasie (ADH) | 20-30% |
| ➤ Lobuläre intraepitheliale Neoplasie (LN/LIN) | 0-10% |
| ➤ Flache epitheliale Atypie (FEA) | 0-10% |
| ➤ Radiäre Narbe / komplexe sklerosierende Läsion | 0-10% |
| ➤ Papillome ohne Atypien | 0-10% |
| ➤ Zellreiche fibroepitheliale Tumore / Phyllodes Tu. | 0% |

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Management nach minimalinvasiver Biopsie

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**Oxford / AGO
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 duktalem 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 Gänge. Die Summe der Durchmesser aller betroffenen Lumina in einer dukto-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- und kontralateral erhöhtes Brustkrebsrisiko: 3 – 5-fach nach 10 Jahren.
- Eine Einteilung in DIN 1 - 3 (duktales intraepitheliales Neoplasie Grad 1 - 3) ist nicht ausreichend validiert.

Strategie nach Diagnose einer ADH in der Nadelbiopsie

**Oxford / AGO
LoE / GR**

ADH in Stanz-/ Vakuumbiopsie:

- Offene Exzisionsbiopsie
- Offene Exzisionsbiopsie verzichtbar, wenn folgende Voraussetzungen erfüllt sind:
 - a) Kein Herdbefund
 - b) Fokale Läsion (≤ 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

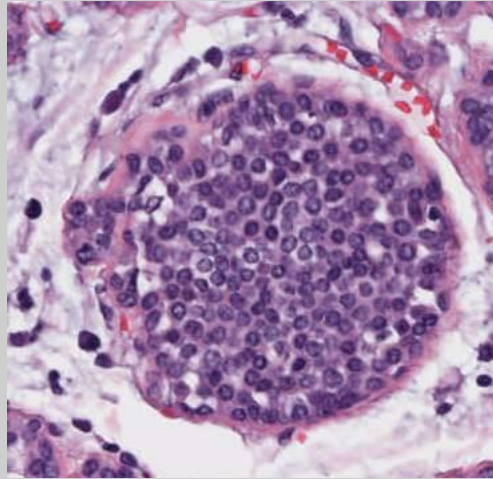
Lobuläre intraepitheliale Neoplasie (LIN)

- 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 Komedotyp-Nekrose werden als maligne klassifiziert → **B5a**
- Indikator-/Vorläufer-Läsion:
Ipsi- und kontralateral erhöhtes Brustkrebsrisiko:
7-fach nach 10 Jahren

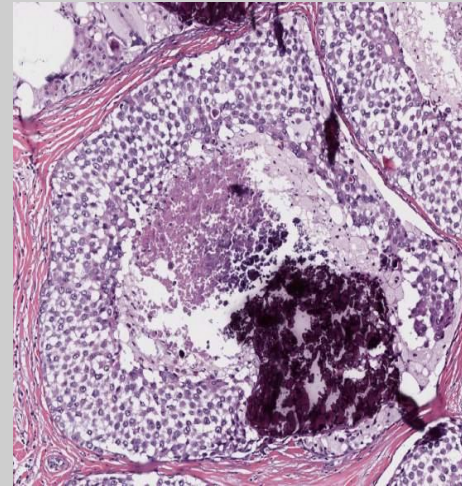
Formen des LCIS

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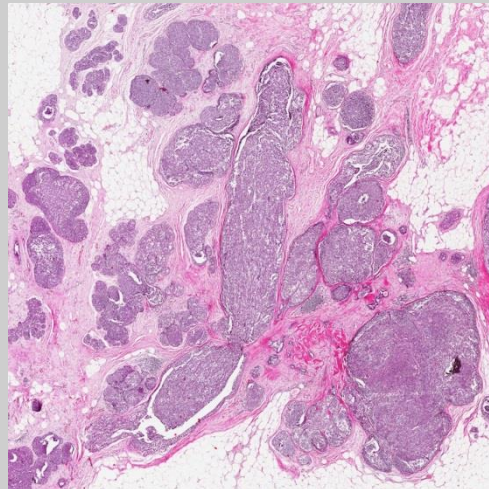
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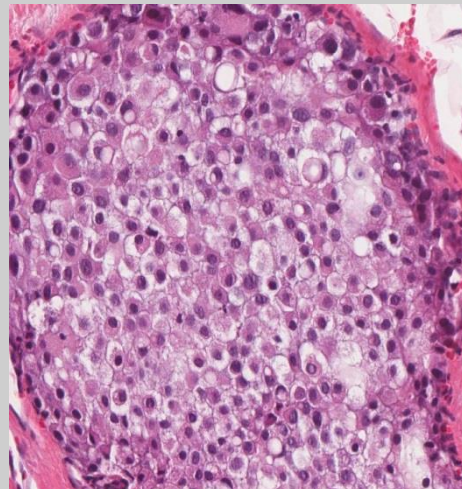
Klass. LIN



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 Komedotypnekrosen, 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 stufenartige Aufarbeitung und die Korrelation des pathologischen Befundes mit der Bildgebung sind 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 duktulolobuläre Einheit

Papillom

- Umfasst: Zentrales und peripheres Milchgangspapillom > 2 mm, Papillom mit Atypien (B3)
- Abzugrenzen von peripheren Mikropapillomen, 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

Oxford / AGO
LoE / GR

- **Solitäres Papillom ohne Atypien in Stanz-/Vakuumbiopsie**
 - Keine weiteren Maßnahmen, wenn Biopsie ausreichend repräsentativ (100 mm²) und keine Diskordanz zur Bildgebung
- **Multiple Papillome**
 - Offene Biopsie
- **Atypisches Papillom in Stanz- / Vakuumbiopsie**
 - Offene Biopsie
- **Papillom am Rand von Resektaten**
 - Keine verfügbaren Daten

3a C ++

3a C ++

3a C ++

Radiäre sklerosierende Läsion

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

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Vorgehen bei radiärer Narbe, komplexer sklerosierender Läsion (CSL)

Oxford / AGO
LoE / GR

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

→ Offene Biopsie

3b C +

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

5a C +

➤ Radiäre Narbe / CSL im Resektionsrand nach Exzisionsbiopsie:

→ 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 Potenzial

**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 Potenzial (Tamoxifen)

NSABP-P1 Study, update 2005

	Placebo Rate / 1000 WE	Tamoxifen Rate / 1000 WE	RR	95% CI
Alle Frauen	6.29	3.59	0.57	0.46-0.70
Mit/ohne LCIS	5.93	3.41	0.58	0.46-0.72
Mit LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
Mit ADH	10.42	2.55	0.25	0.10-0.52
5-Jahresrisiko <2%	4.77	3.18	0.67	0.43-1.01
5 Jahresrisiko > 5%	11.98	5.15	0.43	0.28-0.64
Eine Verwandte 1.Grades	6.47	3.48	0.54	0.34-0.83
Mehr als drei Verwandte 1. Grades	11.24	5.48	0.49	0.16-1.34
Frakturen	2.88	1.97	0.91	0.51-0.92
Endometriumkarzinom	0.68	2.24	3.28	1.87-6.03

Angebote nur für Frauen mit erhöhtem Brustkrebsrisiko (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 Potenzial (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.

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Prävention bei Läsionen mit unsicherem biologischem Potenzial (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 Potenzial (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)

- **Version 2002:**
Gerber
- **Versionen 2003–2015:**
**Audretsch / Blohmer / Brunnert / Costa /
Fersis / Friedrich / Hanf / Junkermann /
Lux / Maass / Möbus / Nitz / Oberhoff /
Scharl / Solomayer / Souchon / Thill /
Thomssen**
- **Version 2016:**
Kühn / Friedrich

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	++

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

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- **108.196 Patientinnen aus der SEER data base**
- **Retrospektive Analyse**
- **Brustkrebsspezifische Mortalität 3.3 %**
- **Erhöht bei jungen Frauen und schwarzer Rasse**
- **Patientinnen mit invasiven Rezidiven haben eine ungünstigere Prognose quoad vitam
HR 18 (95%CI, 14,0-23,6)**
- **Die Reduktion von invasiven Rezidiven durch Radiotherapie verbessert nicht das Überleben nach 10 Jahren**

Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

Treatment	Cases, No	10-Year BCS Mortality (95%CI), %	Univariate HR (95% CI)	P Value	Multivariate ³ HR (95%)	P Value
Lumpectomy						
Without radiotherapy	19762	0.9 (0.7 - 1.1)	1 [Reference]		1 [Reference]	
With radiotherapy	42250	0.8 (0.7 – 1.0)	0.86 (0.67 – 1.10)	0.22	0.81 (0.63 – 1.04)	0.10
all	63319	0.8 (0.7 – 1.0)	1 [Reference]		1 [Reference]	
Unilateral mastectomy	19515	1.3 (1.1 – 1.5)	1.45 (1.18 – 1.79)	< 0.001	1.20 (0.96 – 1.50)	0.11

³ Adjusted for year of diagnosis, age of diagnosis, ethnicity, income, ER-status, tumor size and grade

ORIGINAL ARTICLE – BREAST ONCOLOGY

Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years

Preeti Subhedar, MD¹, Cristina Olcese, BS¹, Sujata Patil, PhD², Monica Morrow, MD, FACS¹, and Kimberly J. Van Zee, MS, MD, FACS¹

Breast Conserving Surgery Alone

Recurrence rate (95 % confidence interval)

Time period	5 year	10 year	HR	P value
1978-1998	19.1 % (15.6 - 23.2 %)	26% (22.0 - 30.7%)	1.0	----
1999-2010	8.9 % (7.1 - 11.3 %)	19% (14.9 – 23.1%)	0.59	0.0002

Breast Conserving Surgery and Radiotherapy

Recurrence rate (95 % confidence interval)

Time period	5 year	10 year	HR	P value
1978-1998	6.4% (4.1- 9.8 %)	13% (9.3 - 17.1 %)	1.0	----
1999-2010	4.9% (3.7 – 6.5 %)	11% (8.7- 14.2 %)	0.84	0.04

Generelle therapeutische Prinzipien

Exzision (BET, Mastektomie) ist die therapeutische Basis für die Behandlung des DCIS.

Die adjuvante Therapie (Strahlentherapie, anti-hormonelle Therapie) muss mit der Patientin auf der Basis einer Risiko-Nutzen Bewertung individuell erörtert werden.

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 Mikrokalzifikationen, 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	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	+/-
➤	MSKCC Nomogram	2b	C	+/-
➤	DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom	3b	C	++
➤	Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)	2b	C	-

Strahlentherapie Statements

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- **Strahlentherapie hat keinen Einfluss auf das Gesamtüberleben.** **LOE 1a**
- **Strahlentherapie reduziert das Lokalrezidivrisiko (invasiv und nicht-invasiv) um 50 %.** **LOE 1a**
- **Das Vermeiden eines invasiven Rezidivs ist sehr wahrscheinlich nicht mit einem Überlebensvorteil verbunden.** **LOE 2b**
- **Der absolute individuelle Benefit der Strahlentherapie ist vom individuellen Lokalrezidivrisiko abhängig.**
- **The number needed to treat (für jedes breast event) ist 9 (über alle Risikogruppen)**

DCIS Strahlentherapie

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Radiotherapie nach:

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

Sonderformen der Radiotherapie:

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

- * NW und Nachteile der Radiotherapie müssen gegenüber der erreichbaren Risikoreduktion abgewogen werden. Ein Verzicht auf eine Strahlentherapie nach BEO bedeutet ein erhöhtes lokales Rezidivrisiko ohne Einfluss auf das Überleben. Dieses gilt auch für Patientinnen mit günstigen prognostischen Faktoren (low-risk-Subgruppe; Level I-Evidenz): < 2,5 cm, low and intermediate nuclear grade, mammographisch entdeckt

** Analyse im Rahmen laufender Studien

Cochrane Analyse

Postoperative Radiatio

(Gesamtkollektiv mit Radiatio nach BEO)

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

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

DCIS

Adjuvante Systemtherapie

- **Antihormonelle Therapie hat keinen Einfluss auf das Gesamtüberleben.** **LOE 1a**
- **Antihormonelle Therapie kann einen geringen Effekt auf die ipsilateralen invasiven Rezidive haben.** **LOE 1a**
- **Antihormonelle Therapie hat einen Effekt auf die kontralaterale invasive Rezidivrate und die ipsilaterale und kontralaterale DCIS-Rezidivrate.** **LOE 1a**
- **The number needed to treat (für jedes breast event) ist 15.** **LOE 1a**

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.**

DCIS

Adjuvante Systemtherapie

**Oxford / AGO
LoE / GR**

- | | | | |
|---|-----------|----------|-------------|
| ➤ Tamoxifen (nur ER+) | 1a | A | +/-* |
| ➤ Aromataseinhibitor (nur ER+) bei
postmenopausalen Patientinnen | 1b | A | +/-* |
| ➤ Trastuzumab (nur HER2+) | 5 | D | -- |

***Indikation zur Therapie ist von Risikofaktoren,
Nebenwirkungen und Patientinnenpräferenz abhängig.**

Lokalrezidiv des DCIS nach Tumorektomie

**Oxford / AGO
LOE / GR**

Nach Radiatio

➤ **Einfache Mastektomie
+ SN B**

3a C +

5 D +

➤ **Sekundäre Tumorektomie**
führt zu Rezidiven in bis zu 30 % der Fälle
(NSABP B17)

5 D +/-

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

- **Versionen 2002–2015:**
**Bauerfeind / Blohmer / Böhme / Costa /
Fersis / Gerber / Hanf / Janni / Junkermann/
Kaufmann / Kühn / Kümmel / Nitz / Rezai /
Simon / Solomayer / Thomssen / Thill /
Untch**
- **Version 2016:**
Brunnert / Solomayer

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Operative Therapie des Mammakarzinoms unter onkologischen Aspekten

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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	+/-

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

** 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.

Perioperatives Staging

**Oxford / AGO
LoE / GR**

➤ Anamnese und klinische Untersuchung

5 D ++

**Nur bei hohem Risiko für Fernmetastasen
und / oder Symptomen:**

➤ Röntgen-Thorax

5 D +

➤ Leberultraschall

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**
- **Die Gesamtüberlebensraten nach MRM und radikaler Mastektomie sind äquivalent**
- **Die Lokalrezidivraten nach „skin sparing mastectomy“ (SSM) und MRM sind äquivalent**
- **Die Erhaltung des Mammillen-Areola-Komplexes (MAK) bei MAK-fernem Tumor und tumorfreiem retroareolärem Gewebe ist onkologisch sicher**

1a A

1b A

2b B

4b C

Brusterhaltende Operation

Vorgehensweise, Technische Aspekte

Oxford / AGO LoE / GR

➤ Nicht palpable Läsionen			
➤ Bildgebend gestützte Drahtmarkierung	2b	B	++
➤ Radionuklidmarkierung	2b	B	+/-
➤ Präparateradiographie oder -ultraschall	2b	B	++
➤ Tumorfrem 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	+/-
➤ Intraop. Schnitttrandbeurteilung mit Margin probe	1b	A	+/-

Brusterhaltende Operation (BEO) ohne neoadjuvante Therapie

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- | | | | |
|---|-----------|----------|------------|
| ➤ 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 (≥ 10LN)			
➤ 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

Vorteil einer Sentinel LN Bestimmung nach der NACT (Neoadjuvante Chemotherapie) (N+) und Empfehlungen zur Durchführung

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- **NACT (+/- Anti-HER 2 Therapie) reduziert die Anzahl befallener axillärer LN um 20->50%**
- **Dadurch Möglichkeit, ALND nach NACT zu vermeiden**
- **SLNB FNR wird durch die Entfernung von >2sn und die gleichzeitige SN-Markierung durch Radiocolloid und Patentblau reduziert**
- **Erwägung einer IHC Bestimmung im SN**
- **Clip-Markierung von positiven LN vor der NACT**

Operative Therapie der Axilla vor und nach NACT

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SLNB vor oder nach NACT bei cN0						
SLNB vor NACT				2b	B	+
SLNB nach NACT*				2b	B	+
Weitere operative Therapie in Abhängigkeit von SLNB						
cN-Status (vor Therapie)	pN-Status (vor Therapie)	cN-Status (nach Therapie)	operatives Vorgehen nach Therapie			
cN0	pN0(sn)	-	Nihil	1a	A	+
cN0	pN+(sn) analog ACOSOG Z0011	ycN0	Nihil Re-SN alleine ALND	3 2b 3	B B B	+/- - +/-
cN0	pN+(sn) nicht analog ACOSOG Z0011	ycN0	Re-SN alleine ALND Axilla XRT	2b 2b 2b	B B B	- + +
cN0	Nicht durchgeführt	ypN0(SN) ycN0 ypN+(SN)	SN alleine ALND ALND	2b 2b 2b	B B B	+/- +/- +
cN+	cN+ (CNB/FNA + Clp Markierung)	ycN0 ycN+ (CNB/FNA)	SN alleine* ALND ALND	2a 2b 2b	B B B	+/- + ++

* Analog ACOSOGZ1071

Sentinel-Lymphknoten-Biopsie (SLNB)

Indikationen I

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	1b	A	++
➤ Klinisch (cN0) / sonographisch neg. Axilla			
➤ Zusätzliche FNA / Stanzbiopsie (klinisch/sonographisch suspekter axillärer Lymphknoten) (plus Clipmarkierung bei Neoadjuvans), um eine SLNB zu ermöglichen	2a	B	+
➤ T 1-2	2b	A	++
➤ T 3-4c	3b	B	+
➤ Multifokales / multizentrisches MaCa	2b	B	+
➤ DCIS	3b	B	+
➤ Mastektomie	3b	B	+
➤ DCIS beim Mann	5	D	+
➤ BET	3b	B	-
➤ MaCa des Mannes	2b	B	+
➤ Bei der älteren Patientin	3b	B	+

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Sentinel-Lymphknoten-Exzision

Indikationen II

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- **Während Schwangerschaft oder Stillzeit (nur Tc, keine Blaumarkierung)**
- **Nach vorausgegangener Tumorektomie**
- **Frühere „große“ Brust-Operation (z.B. Reduktionsplastik, Mastektomie)**
- **Ipsilaterales intramammäres Rezidiv nach vorheriger BET und vorheriger SNE
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	4	D	-
➤ Indocyaningrün (ICG)*	2b	B	+/-
➤ SPIO#	2b	B	+/-

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SPIO: Superparamagnetic Iron Oxide

* Studienteilnahme empfohlen

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	2b	B	++
➤ Beginn der endokrinen Therapie nach OP 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 2002–2015:
**Audretsch / Bauerfeind / Blohmer /
Brunnert / Dall / Fersis / Hanf / Kümmel /
Lux / Nitz / Rezai / Rody / Scharl /
Thomssen**
- Version 2016:
Gerber / Rezai

Definition der onkoplastischen Operation

Der Einsatz plastischer chirurgischer Techniken zum Zeitpunkt der Tumorentfernung, um sichere Resektionsgrenzen zu erreichen und eine ästhetische Brustform zu ermöglichen.

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Onkoplastische brusterhaltende Operation

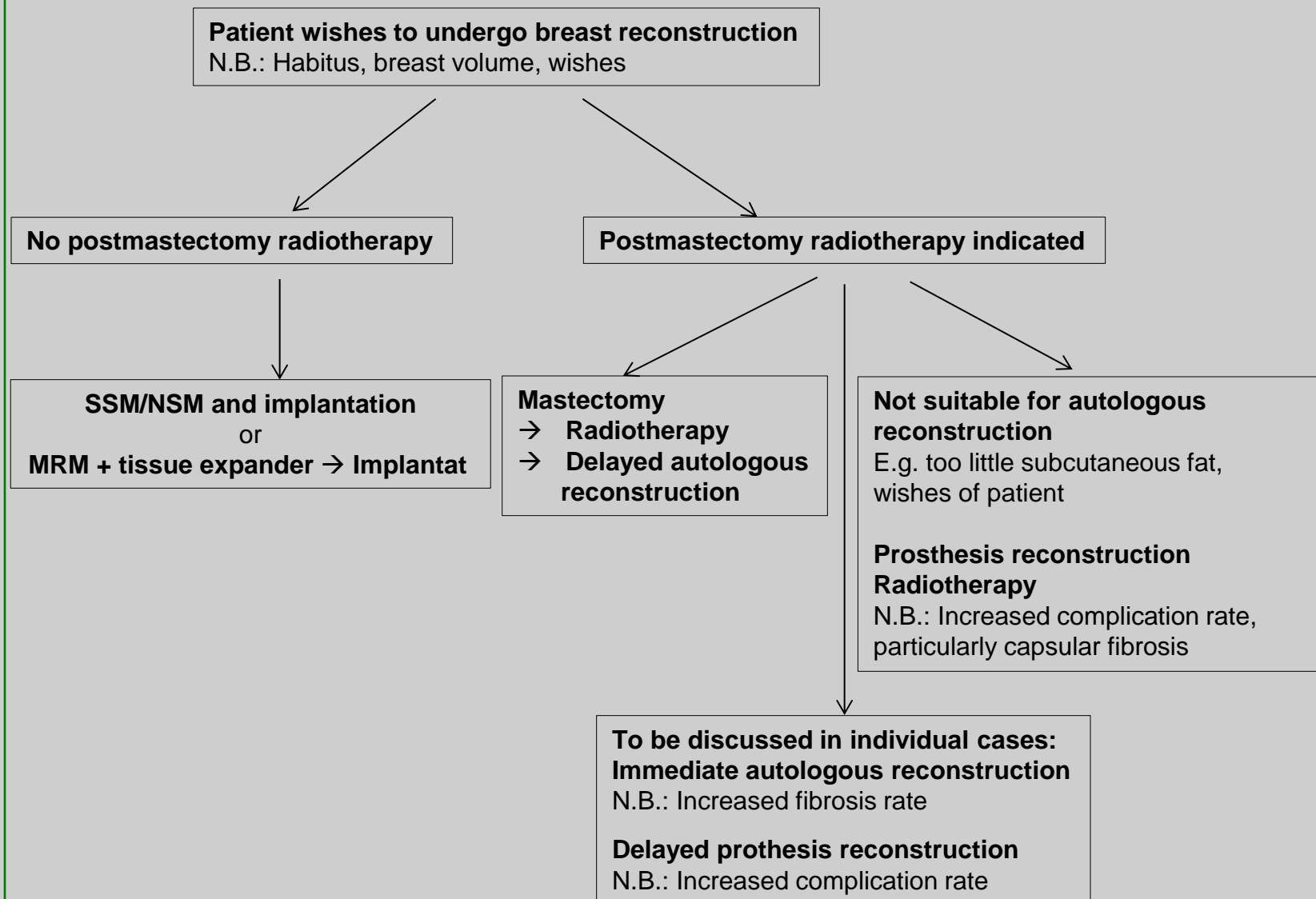
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- | | | | |
|---|-----------|----------|------------|
| ➤ Tumoradaptierte Reduktionsplastik | 2a | B | + |
| ➤ Lokale Lappen-/Verschiebetechniken | 2a | B | + |
| ➤ Partielle Mastektomie mit Gewebstransfer | 3b | B | +/- |

Algorithmus der Brustrekonstruktion



Brust Rekonstruktion

Grundsätze

AGO: ++

- **Beratung hinsichtlich aller Op-Techniken, einschließlich der an der eigenen Klinik nicht angebotenen Techniken, sowie deren Vor- und Nachteile**
- **Möglichkeit zum Einholen einer Zweitmeinung**
- **Besprechung einer neoadjuvanten Systemtherapie bei ungünstiger Tumor-Brust-Relation**
- **Mögliche Angleichung-/Folge-Ops zur Symmetrieherstellung besprechen**
- **Bevorzugung einer die Patientin wenig belastenden Op-Technik mit langfristig stabilem ästhetischen Ergebnis**
- **Cave: keine Verzögerung in der adjuvanten Therapie durch die Rekonstruktion**

Möglichkeiten der Rekonstruktion nach Mastektomie

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➤ 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	+

Zeitpunkt der Rekonstruktion

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- | | 3b | B | ++ |
|---|----|---|-----|
| ➤ Sofortrekonstruktion | | | |
| ➤ Obligat bei SSM/NSM | | | |
| ➤ Vermeiden des Postmastektomie-Syndroms | | | |
| ➤ Intervallrekonstruktion | 3b | B | ++ |
| ➤ Keine Behinderung von adjuvanten Therapien (CHT, RT) | | | |
| ➤ Nachteil: Verlust des Hautmantels | | | |
| ➤ Verzögerte Sofortrekonstruktion („Delayed-immediate BR“) | 3b | B | +/- |

Zeitpunkt der Rekonstruktion mit Implantaten in Bezug zur Strahlentherapie

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➤ Implantat-Rekonstruktion (IR)

- IR ohne Strahlentherapie (RT)
- IR vor RT / nach PBRT
- Cave: hohe Komplikationsrate
- IR nach MX* und RT
- IR nach sekundärer MX (nach BET)
- Perioperativ verlängerte Antibiose
(mindestens 48 Stunden)

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

*MX = Mastektomie

Techniken / Netze im Rahmen der Rekonstruktion

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➤ Eigengewebe (z.B. deepithelialisierter Corium-Fett-Lappen, Lado*)	3b	C	+#
➤ Azelluläre Dermis (ADM)	2b	B	+#
➤ Synthetische Netze zur Muskel-fixierung	2b	B	+#

* Latissimus dorsi Lappen

Teilnahme an Registerstudien empfohlen

Lipotransfer

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- | | | | | |
|---|--|-----------|----------|----------|
| ➤ | 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

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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

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Freier Gewebetransfer

- **DIEP**
- **Freier TRAM**
- **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

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- **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

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LDF* + Implantat

- **Nach RT**
- **Vor RT**

Other flaps + Implantat

2b	C	+
3b	C	+
5	D	-
5	C	+/-

Vorteile:

- **TRAM: bevorzugt Implantateinlage nach Intervall**
- **Verbesserte Abdeckung des Implantates**
- **Geeignet zur Rekonstruktion bestrahlten Gewebes**

Nachteil:

- **Muskelkontraktion (LDF)**

* LDF = Latissimus dorsi flap

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

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➤ 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)

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

*Beratung, Risikoberechnung und Nachsorge in spezialisierten Zentren empfohlen

Formen der Risiko-reduzierenden (bilateralen) Mastektomie (RRBM)

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

➤ Einfache Mastektomie	2b	B	+
➤ RRBM mittels SSM*	2b	C	+
➤ RRBM mittels NSM* (MAK [#] erhaltend)	2b	C	+
➤ Kontralaterale prophylaktische Mastektomie	4	C	+/-

* SSM / NSM: Skin-/Nipple-Sparing Mastectomy

MAK: Mamillen-Areola-Komplex

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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START

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

Adjuvante endokrine Therapie bei prä- und postmenopausalen Patientinnen

➤ **Versionen 2002–2015:**

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

➤ **Version 2016:**

Jackisch / Schneeweiss

Bestimmung des Steroid-Hormonrezeptorstatus

Oxford LoE: 1

GR: A

AGO: ++

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„Endokrines Ansprechen“ (früher rezeptorpositiv):

Immunhistologie (ER und / oder PgR)

0%	pos. Zellen:	endokrin nicht sensitiv
≥ 1-9%	pos. Zellen	endokrin niedrig sensitiv
≥ 10%	pos. Zellen :	endokrin sensitiv

Status unbekannt: endokrin sensitiv

Adjuvante endokrine Therapie

Bestimmung des Menopausenstatus

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Bestimmung des Menopausenstatus:

- **Menstruationsanamnese** **+**
- **FSH, E2** **++**

Adjuvante endokrine Therapie

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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

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

1a A ++

2b C ++

1a A ++

Generelle Prinzipien der adjuvanten endokrinen Therapie

AGO ++

- **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 ein 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 von 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 +/-

* Behandlung so lange tolerabel und 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	+
➤ Reduktion von POF* bedingt durch eine adjuvante Chemotherapie	1b	B	+/-

* POF: Premature ovarian failure

Adjuvante endokrine Therapie bei postmenopausalen Patientinnen

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- **AI für 5 J.**
 - **Präferenz bei lobulären Karzinomen**
 - **Sequentielle Therapie für 5 -10 Jahre**
 - **Tam → AI (2-5 Jahre)***
 - **AI (2-5 Jahre.)* → Tam**
(Präferenz bei N+ Status)
- **Tamoxifen 20 mg/d für 5-10 J.**

1a	A	+
2b	B	++
		++
1a	A	
1b	C	
1a	A	++

*** Dauer der AI Therapie ≤ 5 J.**

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

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➤ **Erhaltung der Ovarialfunktion**

➤ **CHT + GnRHa**

(GnRHa Applikation > 2 Wochen
vor Chemotherapie)

1b B +/-

Beeinflussung des Chemoeffektes nicht sicher ausgeschlossen!

➤ **Beratung über Fertilitätserhaltung**

4 C +

➤ **Fertilitätserhalt mit assist. reprod. Therapie**

(Information: www.fertiprotect.de)

4 C +

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 prädictieren 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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- **Barriere-Methoden**
- **Sterilisation (Tubenligatur / Vasektomie)**
- **Nicht-hormonelle intrauterine devices (IUDs)**
- **Levonorgestrel-releasing IUDs**
 - Entfernung bei Erstdiagnose
- **Timing-Methoden**
- **Ausschließl. Progesteron-Kontrazeptiva (oral / im)**
- **Komb. orale Kontrazeptiva**

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LoE / GR

5	D	+
5	D	+
3b	D	+
2b	C	-
4	D	+/-
5	D	-
5	D	-
5	D	-

Kontrazeptive Notfall-Optionen für Frauen nach Brustkrebs

Oxford / AGO
LoE / GR

➤ **Copper intrauterine devices (Cu-IUD)**

5 D +

➤ **Levonorgestrel, Ulipristal**

5 D +

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.

Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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Autor	Jahr	Odds Ratio (95%CI)	Ereignisse GnRHa	Ereignisse Kontrolle
Gilani ^A	2007	0.06 (0.00, 1.24)	0/15	5/15
Badawy	2009	0.06 (0.02, 0.20)	4/39	26/39
Sverrisdottir_1	2009	0.19 (0.04, 1.06)	14/22	18/20
Sverrisdottir_2	2009	2.03 (0.31, 13.27)	27/29	20/23
Behringer [*]	2010	0.67 (0.08, 5.30)	7/10	7/9
Del Mastro	2011	0.25 (0.12, 0.52)	11/139	31/121
Gerber	2011	0.56 (0.19, 1.62)	9/30	13/30
Demeestere [*]	2012	1.14 (0.38, 3.42)	9/45	7/39
Munster	2012	1.24 (0.19, 8.20)	3/26	2/21
Elgindy_1	2013	0.75 (0.15, 3.79)	3/23	4/24
Elgindy_2	2013	0.63 (0.10, 4.21)	2/23	3/23
M-H Overall (I-squared = 55.8%, p = 0.012)		0.36 (0.25, 0.53)	89/401	136/364
Random Effect Pooled OR		0.43 (0.22, 0.84)		

Vorteil GnRHa / Vorteil Kontrolle

TEXT /SOFT Joint Analysis

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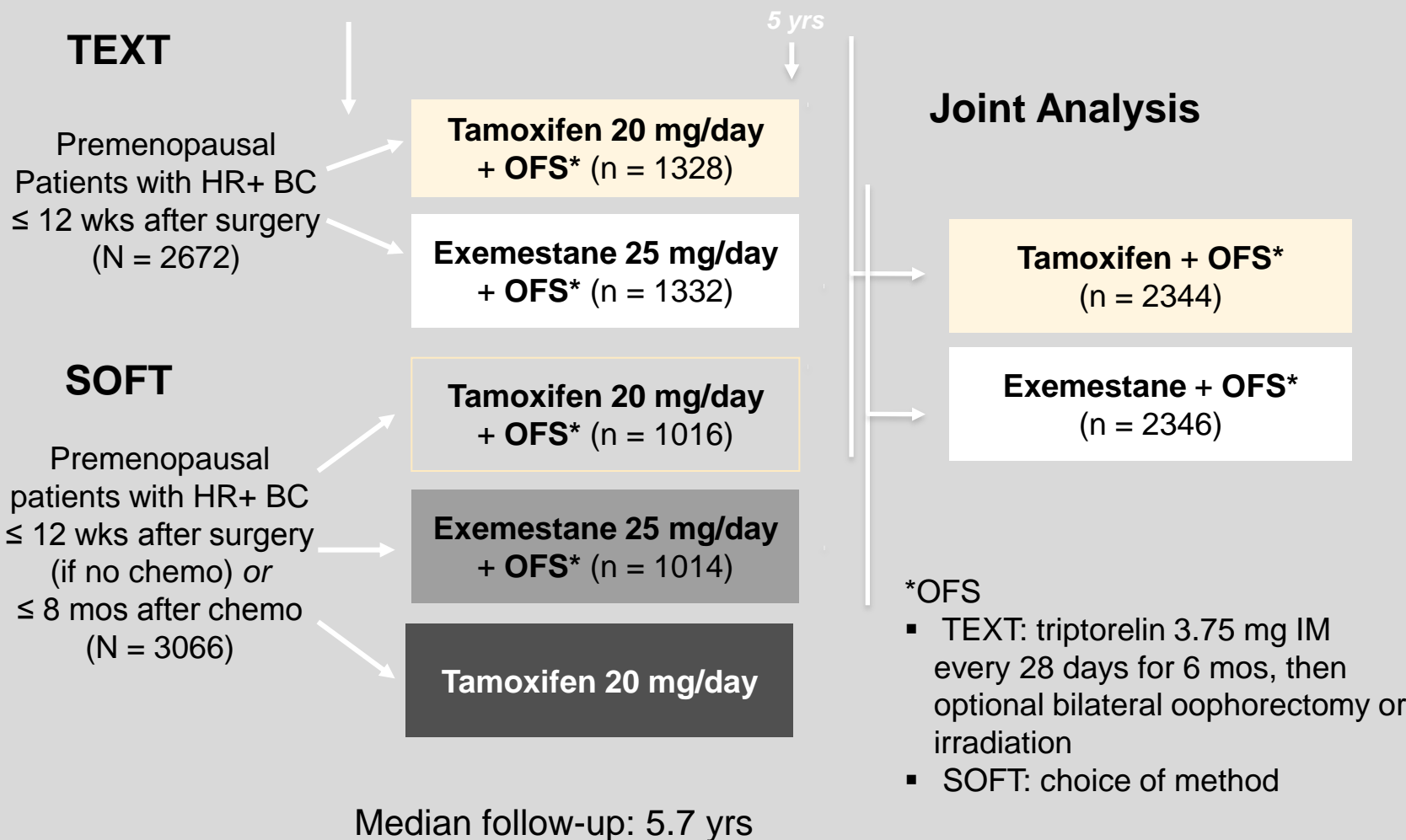
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Further
Information

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Aromatase Inhibitors in Adjuvant Therapy

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Overview over Published Trials: Upfront and Extended Therapy

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

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

Aromatase Inhibitors in Adjuvant Therapy

Overview over Published Trials: Switching/Sequential trials

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Trial	Source	AI	Indication	Pts	F/U mo	DFS/BCFS/TTR/ TTDR/CBC	OS	Side Effects	Remarks
IES	Bliss JM	E	switch after 2-3y T vs T	4599	91	DFS HR 0.76, ITT p<0.01 DFS HR 0.75, ER+/u BCFS HR 0.76, ITT, s BCFS HR 0.75, ER+/u TTDR HR 0.83, ITT, s TTDR HR 0.82 ER+/u, s	HR, 0.86; 95% CI, 0.75 to 0.99; P = .04).	gyn AE T>A TE T>E SE E>T diarrhea E>T	Random after 2-3y T, only pts. relapse-free after 2-3 y T were included
ITA	Boccardo 2006	A	switch after 2-3y T vs T	448	64	EFS HR 0.57, p<0.01 RFS HR 0.56, p=0.01	ns	SAE T>A	Random after 2-3y T, only pts. relapse-free after 2-3 y T were included
ABCSG - 08 ARNO95	Jakesz 2005	A	switch after 2y T vs T	3224	28	DFS HR 0.59, p<0.01 TTR HR 0.60, p<0.01 TTDR HR 0.61, p<0.01	ns	TE T>A SE A>T	
ABCSG -08	Jakesz 2005	A	switch after 2y T vs T	2529	31	DFS HR 0.61, p=0.01 TTDR HR 0.68, p=0.11 CBC HR 0.45, p=0.07	ns	TE T>A SE A>T	Analysis of switch data only, random upfront
ARNO 95	Kaufmann 2007	A	switch after 2y T vs T	979	30	DFS HR 0.66, p=0.049	HR 0.53, p=0.045	SAE T>A 30,8 vs 22,7 %	No chemotherapy, random after 2 y T; only pts relapse-free after 2 y T were included
BIG 1-98	Regan et al 2011	L	switch after 2y T vs. Let switch after 2y L vs. Let.	1548 1540	97	disease-free survival; 87.5%, 87.7%, 85.9% ns	89.9%, 88.7%, 88.1% ns	SE L>T VE L = T	Comparison of switch L/T or T/L vs. L
TEAM	Van de Velde 2011	E	TEAM: E alone vs Tam switch after 2 – 3 y to E	4868 4898	60	hazard ratio 0.97, 95% CI 0.88-1.08; p=0.60)	n.a.	DVT; endometrial > switch Musculoskeleta l problems hyperlipidaemi a > E mono	
N-SAS BC03	Aus Japan 2010	A	Tam 5 y vs Tam→ A switch after 1 – 4 y Tam	706	42	DFS: 0.69 P = 0.14 RFS 0.54 P = 0.06	n.a.	dito	
Meta- analysis									
ARNO95 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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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 2003–2015:**
**Harbeck / Jackisch / Janni / Loibl / Lux /
von Minckwitz / Möbus / Müller / Nitz /
Schneeweiss / Simon / Schütz /
Solomeyer / Stickeler / Thomssen / Untch**
- **Version 2016:**
Möbus / von Minckwitz

Subtyp-spezifische Strategien zur Systemtherapie

AGO

- **Wenn die Indikation zur Chemotherapie aufgrund der Tumorbilogie 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** **+**
 - **Anthrazyklin-freie, Taxan-haltige Therapie bei niedriger Tumorlast** **+**
 - **Dosisdichte, dosis-intensivierte Chemotherapie bei großer Tumorlast** **+**
- **Triple-negativ (TNBC)**
 - **Konventionell dosierte AT-basierte Chemotherapie** **++**
 - **Dosisdichte, dosis-eskalierte Chemotherapie** **+**
 - **Neoadjuvant Platin-haltige 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	E₉₀C q3w x 4 → P₈₀ qw1 x 12	1b^a	B	++
➤ AC → P_w	A₆₀Cq 3w x 4 → P₈₀qw1 x 12	1b	A	++
➤ AC → D	A₆₀C q3w x 4 → D₁₀₀ qw3 x 4	1b	A	++
➤ *EC → D	E₉₀C q3w x 4 → D₁₀₀ qw3 x 4	1b	B	++
➤ DAC	D₇₅A₅₀C q3w x 6	1b	A	++

Anthrazyklin-freie Regime

➤ DC	D₇₅ C₆₀₀ x 4	1b	B	+
➤ Pac mono	P₈₀ q1w x 12	1b	B	+/-
➤ CMF		1a	A	+/-

* Extrapoliert von Studien mit Doxorubicin

Dosis-dichte und/ oder dosis-eskalierte adjuvante Chemotherapie bei hoher Tumorlast

**Oxford / AGO
LoE / GR**

Dosis-dichte Regime

➤ *EC q3w x4 → Pac q1w x 12	1b	B	++
➤ AC q3w x4 → Pac q1w x 12	1b	A	++
➤ AC q2w x4 → Pac q2w x 4	1b	B	+
➤ EC q2w x4 → Pac q2w x 4	1b	A	+
➤ EC q2w x4 → Pac q1w x 12	1b	B	+

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

➤ E-Pac-C q2w	1b	A	++
---------------	----	---	----

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Adjuvante Chemotherapie: andere Medikamente

**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 | - - |

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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
- Kardiale Zeichen und Symptome

LVEF alle 3 Monate

Adjuvante Therapie mit Trastuzumab: Regime

**Oxford / AGO
LoE / GR**

Simultan mit

- | | | | |
|--|-----------|----------|------------|
| ➤ Paclitaxel / Docetaxel nach AC / EC | 1b | A | ++ |
| ➤ P q1w 12 x ohne A bei pT < 3 cm, pN0 | 2b | B | + |
| ➤ Docetaxel und Carboplatin | 1b | A | + |
| ➤ Mit Anthrazyklinen | 2b | B | +/- |
| ➤ Mit Taxan dosis-dicht | 2b | B | + * |

Radiotherapie simultan zu Trastuzumab

2b B +

*** Studienteilnahme empfohlen**

Adjuvante Therapie mit weiteren zielgerichteten Substanzen

Oxford / AGO
LoE / GR

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

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Neoadjuvante (Primäre) systemische Therapie

Neoadjuvante systemische Therapie

- **Version 2002:**
Costa

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

- **Version 2016:**
Liedtke / Untch

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 A/T-basierte Protokolle mit T + H ++
 - Anthrazyklin-frei, mit Carboplatin +
 - Anthrazyklin-freies, taxan-haltiges Regime bei geringer Tumorlast +
 - Dosisdicht und dosiseskaliert in Fällen mit hoher Tumorlast +
- TNBC
 - Konventionell dosierte AT-basierte Chemotherapie ++
 - Dosisdicht und dosiseskaliert +
 - Neoadjuvante Platin-haltige Chemotherapie +

Neoadjuvante systemische Chemotherapie – Klinischer Benefit

Oxford / AGO
LoE / GR

➤ Überleben ist gleich nach neoadjuvanter (präoperativer, primärer) und adjuvanter systemischer Therapie (bei gleichem Regime und gleicher Zyklenzahl)	1a	A	
➤ Pathologische Komplettremission ist mit einem besseren Überleben assoziiert, besonders in Subgruppen (HR+/HER2neg/Grade3, HER2-pos und TNBC)	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 der post-neoadjuvanten Behandlung	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	+
➤ cT1 / cT2-Tumore o. N0 o. G3	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
➤ Multigensignaturen	III	C	B	+/-
➤ Ki-67	I	B	A	+
➤ Tumor infiltrierende Lymphozyten*	I	B	B	+
➤ PIK3CA Mutation	II	B	B	+/-

* Definiert als dichtes lymphozytenreiches, die Tumorzellen umgebendes Binnenstroma außerhalb der Randzone (Lymphozyten >50% der Stromafläche)

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	++
➤ Taxan gefolgt von Anthrazyklin	1a	A	+
➤ Dosisdichte Protokolle (z. B. E -P-CMF, E-P-C)	1b	B	+*
➤ Platinsalze beim TNBC (unabh. des BRCA-Status)	2b	B	+
➤ Nab-Paclitaxel qw anstatt Paclitaxel qw	1b	B	+/-
➤ Bei TNBC Nab-Paclitaxel qw anstatt Paclitaxel qw	2b	B	+

* Studienteilnahme empfohlen

Mögliche carboplatinhaltige Regime in der neoadjuvanten Situation

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Author	Study	Regimen	pCR rate	3-yr EFS rates
Sikov WM, et al. JCO 2015 SABCS 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)	TNBC ± Cb: 72% vs. 77% (HR 0.84 (95%CI 0.58- 1.22)
von Minckwitz G, et al. Lancet Oncol 2014 SABCS 2015	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)	TNBC ± Cb: 76% vs. 86% (HR 0.56 (95%CI 0.33- 0.96))
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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Neoadjuvante systemische Chemotherapie

Empfohlene Methoden zum Messen des Ansprechens

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	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**
- **Lapatinib in Kombination mit Chemotherapie**
- **Lapatinib + Trastuzumab in Kombination mit Chemotherapie**
- **Pertuzumab + Trastuzumab in Kombination mit Chemotherapie**
- **Zwei gegen HER2 gerichtete Substanzen ohne Chemotherapie**

1b A ++

1a B -

1a B +/-

2b B +

2b B +/-

Neoadjuvante zielgerichtete Therapie bei HER2-negativen Tumoren

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Chemotherapie in Kombination mit Bevacizumab

- **Beim Hormonrezeptor-positiven**

Mammakarzinom

1b B -

- **Beim TNBC**

1b B +/-

Neoadjuvante systemische Therapie

Vorgehen bei einem frühen Ansprechen

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

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

1b A ++

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**

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2b C ++

2b B +

2b B +

1b B +

Bei Progression:

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

4 D ++*

4 D +/-*

***Studienteilnahme empfohlen**

Neoadjuvante systemische Therapie

Lokoregionäre Operationen

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- | | | | |
|---|-----------|----------|-----------|
| ➤ Intraoperative Clipmarkierung
der Tumorregion | 5 | D | ++ |
| ➤ Adäquate Operation nach NST | 2b | C | ++ |
| ➤ Mikroskopisch freie Absetzungsränder | 5 | D | ++ |
| ➤ Exzision innerhalb neuer Grenzen
nach aktueller Bildgebung | 3b | C | + |

Axilläre Intervention vor und nach NACT

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SLNB vor oder nach NACT bei cN0

SLNB vor NACT
SLNB nach NACT

2b
2b
B
B
+
+

Weiteres operatives Vorgehen in Abhängigkeit des SLNB-Status

cN-Status (vor NST)	pN-Status (vor NST)	cN-Status (nach NST)	Operatives Vorgehen (nach NST)			
cN0	pN0(sn)	-	nihil	1a	A	+
cN0	pN+(sn) (analog ACOSOG Z0011)	ycN0	nihil Re-SLNB allein ALND	3 2b 3	B B B	+/- - +/-
cN0	pN+(sn) (not analog ACOSOG Z0011)	ycN0	Re-SLNB allein ALND Axilla XRT	2b 2b 2b	B B B	- + +
cN0	(nicht durchgeführt)	ycN0	SLNB allein ALND	2b 2b	B B	+/- +/-
			ALND	2b	B	+
cN+	cN+ (CNB/FNA + Clip- Markierung)	ycN0 ycN+	SLNB allein* ALND ALND	2b 2b 2b	B B B	+/- + ++

* Analog ACOSOG Z1071

Neoadjuvante systemische Therapie

Indikationen für Mastektomie

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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

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➤ Operation

4 C ++

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

- Radiotherapie innerhalb von
2–3 Wochen nach Operation

2b B ++

Adjuvante systemische Therapie nach neoadjuvanter systemischer Therapie

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- | | | | |
|--|-----------------|---|-----|
| ➤ Endokrine Therapie bei endokrin-sensitiver Erkrankung | 1a | A | ++ |
| ➤ Komplettierung der Trastuzumab-Behandlung auf bis zu 1 Jahr bei HER2-positiver Erkrankung | 2b | B | ++ |
| ➤ Komplettierung der Pertuzumab-Therapie über 1 Jahr bei HER2-positivem Mammakarzinom | 3 | C | - |
| ➤ Bei ungenügendem Ansprechen (d.h. non-pCR (invasive Tumorzellen in Brust und / oder Axilla) nach adäquater NACT (Anthrazykline, Taxane, 18 Wochen) | | | |
| ➤ Capecitabin adjuvant | 1b ^a | B | +/- |
| ➤ Weitere Chemotherapie | 3 | C | - |
| ➤ Experimentelle Behandlung | 5 | D | + |

Neoadjuvante endokrine Therapie

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➤ Postmenopausale Patienten

- Mit endokrin sensiblen Mammakarzinomen, die inoperabel sind und keine Chemotherapie möchten / haben können
- Verbessert die Optionen für brusterhaltende Operationen bei postmenopausalen Frauen mit endokrin sensiblen Mammakarzinomen
- Aromataseinhibitoren (für > 3 Monate)
- Aromataseinhibitor + Lapatinib (HER2+)

➤ Prämenopausale Patientinnen

- Mit endokrin sensiblen Mammakarzinomen, 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)

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2a	B	+
1b	A	+
1a ^a	B	+
2b	B	+/-
5	C	+
2b	C	+
1b	C	+/-
1b	A	-
1b	B	+

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Adjuvante Strahlentherapie



Adjuvante Radiotherapie (RT)

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- **Versionen 2002 – 2015:**
**Blohmer / Budach / Friedrichs / Göhring /
Janni / Kühn / Möbus / Scharl /
Seegenschmiedt / Souchon / Thomssen /
Untch / Wenz**

- **Version 2016:**
Thomssen / Budach / Wenz

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**

Guidelines and Opinions

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St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:

Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractionated regimens involving 15 or 16 fractions are now widely accepted as standard of care.**

St. Gallen 2015: Gnant M, Breast Care 2015;10:124:

With respect to **hypofractionated** breast irradiation after breast conserving surgery, the panel felt that this is **appropriate for patients aged 50+** without chemotherapy or axillary involvement (89% Yes, 2% No, 9% Abstain), but **also for patients younger than 50 years** (71% Yes, 2% No, 27% Abstain), with uncertainty about patients with prior chemotherapy or axillary lymph node involvement (51% Yes, 18% No, 31% Abstain).

Statement J Harris, Dana Farber, Boston, SABCS 2015, PL1-01:

With regard to **hypofractionated whole breast irradiation**, cosmetic results are clearly better, patient satisfaction is improved, uncertainty about use in nodal RT. **We are using it just in about all (266 cGy x 15 with boost in about ½).**

Radiotherapie (RT) nach brusterhaltenden Operationen (BEO; invasive Karzinome): - Bestrahlung der Brust -

LoE 1b B

AGO ++

< 50 Jahre	Hypofraktionierte RT mit sequentielltem Boost oder konventionelle RT (25-28 Fraktionen) mit integriertem oder sequentielltem Boost
≥ 50 Jahre	Niedriges Risiko*: hypofraktionierte RT ohne Boost (15-16 Fraktionen) Hohes Risiko: RT wie für <50 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)

***wie Definition zur Boost-Bestrahlung**

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)

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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	A	+/-

Erhöhung des Lokalrezidivrisikos, aber ohne Einfluss auf Gesamtüberleben; Verminderung der Toxizität; im Falle eines Rezidives kurative Option durch sekundäre Mastektomie und Strahlentherapie

*** Alter ≥ 70 J., pT1, pN0, HR-pos., G1-2, HER2-negativ, Resektionsrand >1 mm**

¹Unterschiedliche Bewertung der publ. 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-free ($\Delta=8\%$)	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; n.s.)
Distant metastasis-free	95% (91% - 97%)	95% (92% - 97%)	HR=1.20 (95% CI, 0.63 to 2.32; n.s.)
Overall survival	66% (61% - 71%)	67% (62% - 72%)	HR=0.95 (95% CI, 0.77 to 1.18; n.s.)

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

Boost und Teilbrustbestrahlung nach BEO beim invasiven Karzinom

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➤ Boost-RT des Tumorbettes (verbesserte lokale Kontrolle, kein Überlebensbenefit)

➤ < 40 Jahre

1b B ++

➤ 40 - 60 Jahre

1b B +

➤ > 60 Jahre, G3 oder >pT1

2b B +/-

➤ Intraoperative Radiotherapie (intraop. APBI)

➤ Als Boost-Bestrahlung vor Ganzbrust-RT

2a B +

➤ Als alleinige Radiotherapie-Maßnahme (IORT 50 kV, IOERT)**

➤ >50 Jahre **

1b B +/-*

➤ >70 Jahre**

1b B +

➤ Postoperative Teilbrustbestrahlung als alleinige Radiotherapie-Maßnahme bei ausgewählten Pat. (APBI)

➤ Interstitielle Brachytherapie

1b B +/-*

➤ >70 Jahre**

1b B +

➤ Intrakavitäre Ballontechnik

2b B -*

➤ IMRT***

2b B -*

*Studienteilnahme empfohlen; **nur bei pT1 pN0 R0 G1-2, HR+, nicht-lobulär, >50 J., kein extensives DCIS, IORT während des ersten Eingriffs; ***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.)
<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)

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

EORTC 22881-10882: Boost vs no Boost

(Endpoint: any first recurrence)

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@15 yrs/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 Any First Recurrence</u>				
All patients (Δ≥4%)	@15y	28.1%	32.1%	HR=0.92 (0.81-1.04), n.s.
	@20y	32,8%	38.7%	
≤40 years (Δ>6%)	@15y	41.5%	48.1%	HR=0.80 (0.56-1.15) , n.s.
	@20y	49.5%	56.8%	
41–50 years	@15y	34.0%	35.6%	HR=0.91 (0.71-1.16), n.s.
	@20y	38.6%	44.2%	
51–60 years	@15y	28.5%	28.7%	HR=0.96 (0.76-1.21), n.s.
	@20y	34.7%	36.2%	
>60 years	@15y	27.4%	29.1%	HR=0.94 (0.74-1.19), n.s.
	@20y	32.1%	32.8%	

(Median F/U 17.2 y) acc. Bartelink et al. Lancet Oncol 2015; 16: 47–56. Suppl.

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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Axilläre Dissektion oder RT der Axilla bei 1-2 pos. SLN:

	Oxford / AGO LoE / GR		
➤ BET und ACOSOG Z0011-Kriterien erfüllt	1b	B	+/-*
➤ Keine weitere axilläre Intervention	1b	B	+/-
➤ Mastektomie (ME), RT der Thoraxwand indiziert und ACOSOG Z0011-Kriterien erfüllt	5	D	+/-*
➤ Keine weitere axilläre Intervention	5	D	+/-
➤ BET und ACOSOG Z0011-Kriterien nicht erfüllt	1b	B	++*
➤ RT der Thoraxwand nach Mastektomie indiziert und ACOSOG Z0011-Kriterien <u>nicht</u> erfüllt oder RT der Thoraxwand nach ME <u>nicht</u> geplant	1b	B	++

>=3 pos. SLN

➤ Axilläre Dissektion	1b	B	++
➤ Radiotherapie der Axilla	1b	B	+

*Studienteilnahme empfohlen

Radiotherapie (RT) anderer locoregionärer Lymphabflussregionen (SCG/ICG)

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RT der supra-/infraklavikulären Lymphregion

- ≥ pN2a oder Level III befallen
- pN1a hohes Risiko*
 - *zentraler oder medialer Sitz und (G2-3 oder ER/PgR-negativ)
 - * prämenopausal, lateraler Sitz und (G2-3 oder ER/PgR-negativ)
- pN0 prämenopausal, hohes Risiko**
 - **zentraler oder medialer Sitz, und G2-3 und ER/PgR-negativ

Oxford /AGO
LoE / GR

1b	A	++
2a	B	+

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

- Nach NACT/NAT (Indikationen wie für eine PMRT)

AGO ¹	2b	B	+/-
------------------	----	---	-----

- Nach NACT/NAT wenn cN+ (Indikationen gemäß PMRT)

DEGRO ¹	2b	A	+
--------------------	----	---	---

¹ Unterschiedliche Bewertung der publizierten Daten durch AGO und DEGRO

Radiotherapie (RT) anderer lokoregionärer Lymphabflussregionen (IMN)

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Mammaria interna Lymphknotenregion (IMN)

➤ **pN0 prämenopausal, hohes Risiko*****
***zentraler oder medialer Sitz und G2-3 und ER/PgR-negativ

➤ **pN1a hohes Risiko***
*zentraler oder medialer Sitz, und (G2-3 oder ER/PgR-negativ)
*lateraler Sitz, prämenopausal und (G2-3 oder ER/PgR-negativ)

➤ **pN2a hohes Risiko****
**G2-3 oder ER/PgR-negativ

➤ **pN1b-c, pN2c, pN3b**

➤ **IMC-RT, bei kardialem Risiko oder bei Gabe von Trastuzumab**

Nach NACT/NAT (Indikation wie für PMRT) AGO¹

➤ **Nach NACT/NAT bei cN+ (ind. acc. PMRT) DEGR0¹**

**Oxford /AGO
LoE / GR**

1b B +/-

2a B +

2a B +

2a B +

2b A --

2b B +/-

2b A +

¹ Unterschiedliche Bewertung der publizierten Daten durch AGO und DEGR0

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 (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

**Oxford / AGO
LoE / GR**

- **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.**

Interaktion zwischen Rauchen und Nebenwirkungen der Strahlentherapie

Oxford / AGO
LoE / GR

- **Erhöhtes Risiko für Lungenkarzinom nach Strahlentherapie wegen Mammakarzinom** **1a A**
- **Die Patientinnen sollten über dieses Risiko informiert werden** **++**
- **Den Patientinnen sollte empfohlen werden, das Rauchen zu beenden** **++**

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Nebenwirkungen der Therapie

START

Nebenwirkungen der Therapie

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- **Versionen 2004–2015:**
**Albert / Bischoff / Brunnert / Costa / Dall /
Friedrich / Friedrichs / Gerber / Göhring /
Huober / Jackisch / Lisboa / Lück / Müller /
Nitz / Schmidt / Souchon / Stickeler /
Untch**
- **Version 2016:**
Lück / Bischoff

Toxizitäts-Beurteilung

Akute Toxizität nach WHO¹ oder NCI-CTC²

Grad

0 keine
1 mild
2 mäßig
3 ausgeprägt
4 lebensbedrohlich

Notwendige Informationen

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

Langzeittoxizität

**Keine allgemeines kategorisiertes
Bewertungssystem**

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

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

Chemotherapie – Akute Toxizitäten I

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

Chemotherapie – Akute Toxizitäten II

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	Allergie	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				++		

ASCO Guidelines PNP

VOLUME 32 • NUMBER 18 • JUNE 20 2014

JOURNAL OF CLINICAL ONCOLOGY

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.

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

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	-

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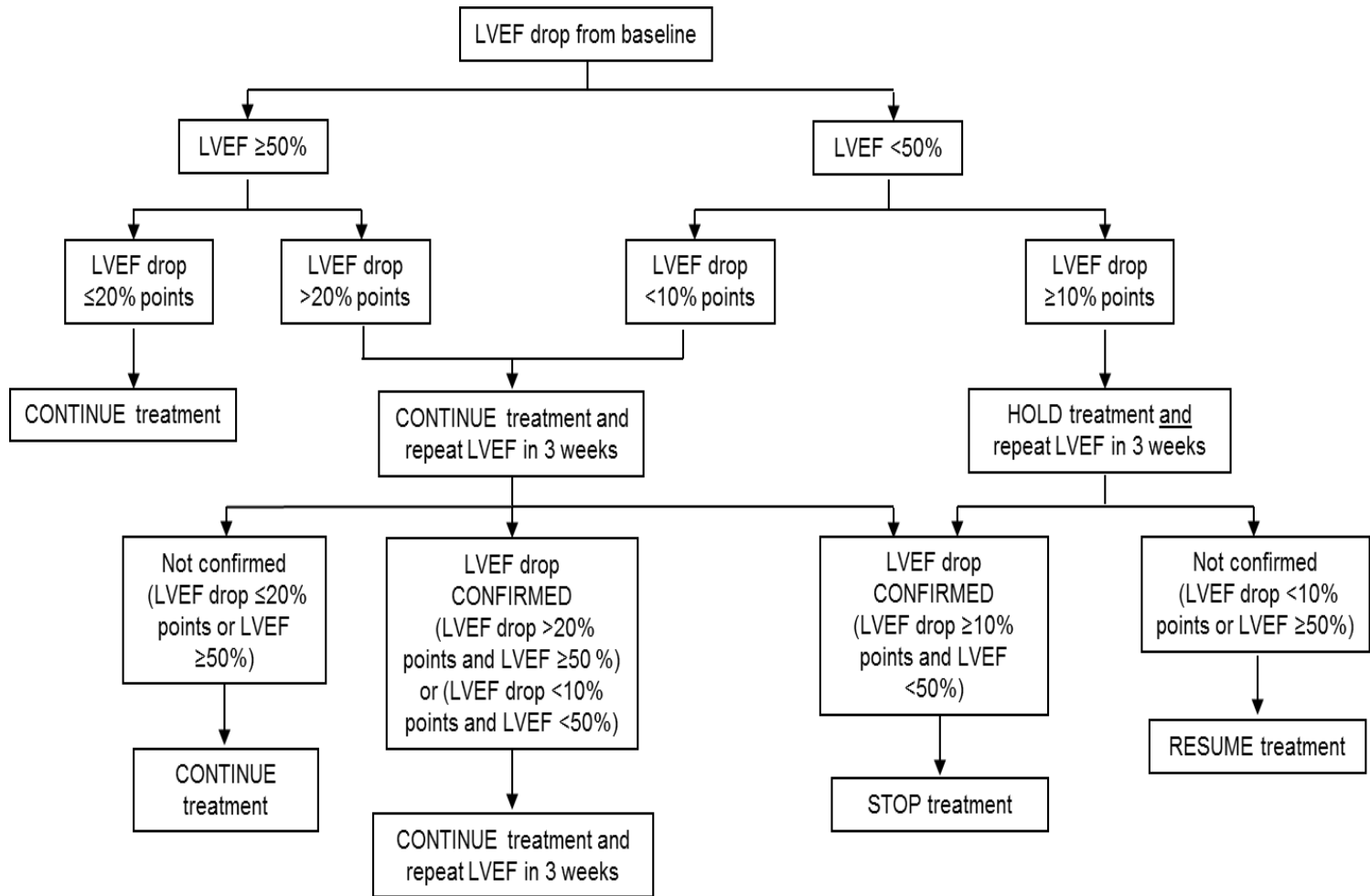
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Nebenwirkungen Trastuzumab/Pertuzumab

Algorithmus bzgl. kardialer Toxizität

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Sekundäre Malignome I

Oxford LoE / GR

- Die Induktion von soliden, malignen Tumoren durch Chemotherapie ist selten 2a
- Alkylantien erhöhen dosisabhängig das Risiko für Leukämien auf 0,2 – 0,4 % innerhalb von 10 - 15 Jahren 2a
- Anthrazyklinhaltige Regime erhöhen das Risiko für MDS und Leukämie auf 0,2 – 1,7 % innerhalb von 8 - 10 Jahren 2a
- PARP-Inhibitoren sind assoziiert mit einem erhöhten Risiko für AML und MDS von 0.5-1% 2b
- Radiotherapie erhöht das Risiko einer Leukämie bei Pat. mit einer anthrazyklinhaltigen Therapie um 0,2 – 0,4 % 2b
- Tamoxifen verdoppelt das Risiko für die Entwicklung eines Endometriumkarzinoms 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**
- **Die Ovarialreserve der nach Chemotherapie prämenopausal gebliebenen Frauen ist reduziert**
- **CRA ist mit verbessertem Outcome (DFS/OS) verbunden**

2b

2b

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 | + |

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(Therapie assoziierte) Schlafstörungen

Oxford / AGO
LoE / GR

- **Schlafstörungen häufig bei Mammakarzinompatientinnen während und nach Therapie beschrieben (20-70%)**
- **Verhaltenstherapie ist effektiv in der Behandlung von Schlafstörungen und Steigerung der Lebensqualität**

2a B

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

1b

1b

1b

2b

Bei adjuvanter Bisphosphonattherapie wurden, außer Akute-Phase-Reaktionen, keine gravierenden Nebenwirkungen 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

Immun-Checkpoint Inhibitoren

➤ Therapeutische Ansätze (Antikörper)

➤ PD1 /PD-L1

➤ Nivolumab

➤ Pembrolizumab

➤ Atezolizumab

➤ CTLA-4

➤ Ipilimumab

Immun-Checkpoint Inhibitoren

➤ Nebenwirkungen \geq Grad 3

- Diarrhoe
- Fatigue
- Colitis
- Hypophysitis
- Hepatitis
- Hautveränderungen
- Thyreoiditis

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Supportive Therapie

Supportive Therapie

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➤ **Version 2002:**
Diel

➤ **Versionen 2003–2015:**
**Bauerfeind / Bischoff / Costa / Dall / Diel /
Fersis / Hanf / Heinrich / Jackisch /
von Minckwitz / Möbus / Oberhoff / Rody
/ Schaller / Scharl / Schmidt / Schütz**

➤ **Version 2016:**
Diel / Möbus

Leitlinien – Umfeld

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

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

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

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

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):

„Supportive Therapie bei onkologischen Patientinnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, final consensus Nov 2015, planned release: 31.5.2016

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

Relevante Leitlinien

- **Rodgers GM, 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**

**Oxford / AGO
 LoE / GR**

5 D +

1a B -

1a A ++

1a B +/-

5 D -

1a A ++

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*** 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

Oxford / AGO
LoE / GR

- **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 A ++

1a A +/-

1b A ++

1b A ++

1b A ++

Relevante Leitlinien

- **Crawford et al: Myeloid Growth Factors. J Natl Compr Canc Netw:1266-1290, 2013**
- **Thomas J. Smith, Kari Bohlke, Gary H. Lyman et al. Recommendations for the use of WBC Growth factors: American society of clinical practice guideline update. J Clin Oncol 2015;28:3199-3212**
- **Volovat C, Bondarenko IM, Gladkov OA et al. Phase III randomized double-blind placebo-controlled, multicentre study of lipegfilgrastim in patients with non-small lung cancers receiving myelosuppressive therapy. SpringerPlus 2015;4:316**

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 $< 500 \text{ cells/mm}^3$)

**Oxford / AGO
LoE / GR**

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

Empirische Antibiotikatherapie

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

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

Dexrazoxane

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

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- **Therapie von Anthrazyklin-Paravasaten**
- **Bei bestehenden kardialen Risiken
alternative Chemotherapie erwägen
(Anthrazyklin-frei, liposomal)**

2b B ++

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	++
➤ Feste Kombination mehrerer Substanzen	1b	A	++
➤ Metoclopramid	3b	C	+

www.ago-online.de

**FORSCHEN
LEHREN
HEILEN**

Supportive Therapie

Antiemetika

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Hesketh, Paul J, Bohlke K, Lyman GH et al. Antiemetics: American society of clinical oncology focused guideline update. J Clin Oncol 2016;34:381-6

Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy induced nausea and vomiting. Ann Oncol 2015;26:1081-90.

Hesketh PJ, Aapro M, Jordan K et al. A review of NEPA, a novel fixed antiemetic combination with the potential for enhancing guideline adherence and improving control of chemotherapy-induced nausea and vomiting. Biomed Res Int 2015;65:1879

Schwartzberg LS, Rugo HS, Aapro M. New and emerging therapeutic options for the management of chemotherapy-induced nausea and vomiting Clin Adv Hematol Oncol 2015;15(3 Suppl. 3):3-13

Jordan K, Schaffrath F, Jahn F et al. Neuropharmacology and management of chemotherapy-induced nausea and vomiting in patients with breast cancer. Breast Care 2014;9:246-53

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	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		
Benzodiazepine	Diazepam Lorazepam	bis zu 20 mg/d 0,5-1,0 mg/d	Sedation, Atemdepression	gering
NEPA (Netupitant and Palonosetron)	fixe Kombinations partner (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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- **Versionen 2005-2015:**
**Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Harbeck / Huober / Janni / Loibl /
Lück / Lux / Maass / Mundhenke / Oberhoff /
Rody / Scharl / Schneeweiss / Solomayer**
- **Version 2016:**
Harbeck / Thomssen

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 Phylloides-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 Chemotherapie-induzierte temporäre Amenorrhoe**
- **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 | 4 | C | ++ |
| ➤ Staging: Ultraschall, Röntgen-Thorax, wenn indiziert | 5 | D | +/- |
| ➤ OP wie bei Nicht-Schwangeren | 4 | C | ++ |
| ➤ Sentinel-Node Biopsie (SLNE; nur Technetium) | 4 | C | + |
| ➤ SLNE 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, Denosumab**

**Oxford / AGO
LOE / GR**

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

Brustkrebs in der Schwangerschaft*

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	Oxford / AGO LOE / GR		
➤ Entbindung erst bei ausreichender kindlicher Reife (iatrogene Frühgeburtlichkeit vermeiden)	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	++

Brustkrebs während Schwangerschaft / Stillperiode*: Prognose

**Oxford
LoE**

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➤ Mammakarzinom während Schwangerschaft / Stillzeit

➤ Adäquate Behandlung ist essentiell

3a

➤ Schwangerschaft / Laktation nach Mammakarzinom

➤ Prognose wird nicht verschlechtert

3a

Geriatrische Einschätzung

- **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 Hilfsdienstleistern**
- **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**
 - **Geriatric Prognostic Index (GPI), 3 Parameter bei onkologischen Patienten (Akuterkrankung oder psychische Belastung, >3 rezeptierte Medikamente, neuropsychologische Probleme)**

Behandlung der „rüstigen älteren“ Patientin

(Lebenserwartung > 5 Jahre und akzeptable Komorbidität)

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➤ **Geriatrische Einschätzung**

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 (insbesondere pN+, ER/PgR-neg.)**

2a C +*

➤ **Radiotherapie**

1a A +

➤ **Hypofraktionierung oder alleinige IORT / IOERT**

1b B +

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

AGO

1b A +

DEGRO

1b A +/-

➤ **Trastuzumab**

2b C +

*Studienteilnahme wird empfohlen

** > 70 Jahre, low risk, hormonsensibler Tumor und endokrine Behandlung (AI oder Tam); CAVE erhöhtes Lokalrezidivrisiko

Unterschiedliche Bewertung der publizierten Daten durch AGO und DEGRO

Therapie der „gebrechlichen älteren“ Patientin

(Lebenserwartung < 5 Jahre, erhebliche Komorbiditäten)

Oxford / AGO
LOE / GR

➤ **Reduzierte Standardtherapie**

2b C ++

➤ **Therapieoptionen abgeleitet aus Studien mit älteren Patientinnen:**

➤ **Keine Brustoperation (endokrine Therapieoption erwägen)**

2b C +

➤ **Keine Axilla-Op. (≥ 60 J., cN0, Rez. pos.)**

2b B +

➤ **Keine Radiatio (≥ 65 J., pT1, pN0, Rez. pos.)**

1b B ++

➤ **Hypofraktionierte Radiatio oder IORT / IOERT als alleinige RT-Maßnahme**

1b B +

➤ **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 ist eine Option (Tumor-Brust-Relation!)
 - Sentinel-Node Biopsie (SNE)
- **Radiotherapie wie bei Frauen**
(beachte Tumor-Brust-Relation!)
- **Genetische Beratung, falls ein(e) weitere(r)**
Verwandte(r) betroffen (MammaCa, OvarialCa)
 - Genetische Beratung ohne familiäre Belastung
- **Früherkennungsuntersuchung für Zweitkarzinome**
nicht vergessen (gemäß Leitlinien)

Oxford / AGO

LOE / GR

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

* Teilnahme an Registerstudie wird empfohlen

Mammakarzinom des Mannes: Systemtherapie

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- | | | | |
|--|-----------|----------|------------|
| ➤ Adjuvante Chemotherapie wie bei Frauen | 2a | B | ++ |
| ➤ HER2-gerichtete 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**

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)

- | | | | |
|---|-----------|----------|------------|
| ➤ Überlebensvorteil durch trimodale Therapie (NACT, MRM, RT) | 2b | B | ++ |
| ➤ Staging | 2c | B | ++ |
| ➤ Hautbiopsie (mind. 2; Detektionsrate jedoch < 75%) | 2c | B | + |
| ➤ Präoperative Chemotherapie | 2c | B | ++ |
| ➤ Regime wie nicht inflammatorisches MaCa:
 Anthrazyklin- und Taxan-basiert | 2b | B | ++ |
| ➤ Bei HER2 + Hinzunahme von Trastuzumab | 2b | B | ++ |
| ➤ Bei HER2 + Hinzunahme von Trastuzumab & Pertuzumab | 2b | B | ++ |
| ➤ Bei HER2 + Hinzunahme von Bevacizumab | 2b | C | +/- |
| ➤ Mastektomie nach Chemotherapie | 2c | B | ++ |
| ➤ Brusterhaltende Therapie im Fall von pCR | 2b | C | +/- |
| ➤ Sentinel-Node-Biopsie alleine | 3b | C | - - |
| ➤ Radiotherapie (PMRT) | 2c | B | ++ |
| ➤ Postoperative Systemtherapie wie nicht inflammatorisch | 4 | C | ++ |

Benefit from Trimodal Treatment in Inflammatory Breast Cancer

Median survival probability		
Trimodal therapy	72 months	p<0.05
Surgery alone	26 months	

Overall survival-probability (OS)	10 years-OS	5 years-OS
Trimodal therapy	55.4%	37.3%
Surgery & chemotherapy	42.9%	28.5%
Surgery & radiotherapy	40.7%	23.5%
Surgery alone		16.5%

Multivariate analysis of OS	Hazard Ratio	95% CI
Surgery & chemotherapy & RT (trimodal therapy)	1.00	-
Surgery & chemotherapy	1.64	1.46 to 1.84
Surgery & radiotherapy	1.47	0.96 to 2.24
Surgery alone	2.28	1.80 to 2.89

Rueth et al. J Clin Oncol 2014; 32:2018-2024

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 (e.g. CUP-Print™)**
- **ER, PgR, HER2**
- **Axilladisektion**
- **Systemtherapie entsprechend N+ Mamma-Ca**
- **Mastektomie bei unauffälligem MRT**
- **Brust-Bestrahlung bei negativem Mamma-MRT**
- **Bestrahlung der regionären LK entsprechend Leitlinien (AGO)**

**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 alleine, 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**
- **Präop. MRT zur Bestimmung der Tumorausdehnung**
- **Diagnose durch Stanzbiopsie**
- **Diagnose durch Feinnadelbiopsie**
- **Staging (CT Thorax, Abd.; bei Angiosarkom MRI Kopf)**
- **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, wenn high risk (Grade II-III, Größe > 5 cm, R1)**
- **Regionale Hyperthermie (Verbesserung lokale Kontrolle z.B. bei Angiosarkom) plus Chemotherapie und/oder Radiotherapie**

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	+/-
2b	B	+

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***Behandlung in spezialisierten Zentren empfohlen**

Sarkome / Angiosarkome der Brust

Therapie von Lokalrezidiven und Metastasen

Oxford / AGO
LOE / GR

Therapie des Lokalrezidivs:

- | | | | |
|--|---|---|-----|
| ➤ R0-Resektion | 4 | C | ++ |
| ➤ Radiotherapie, Chemotherapie nach R1-Resektion | 4 | C | +/- |

Fernmetastasierung / nicht resektable Tumoren:

- | | | | |
|--|----|---|-----|
| ➤ Therapie wie Weichteilsarkome | 4 | C | ++ |
| ➤ Paclitaxel weekly / liposomales Doxorubicin (bei Angiosarkomen) | 2b | B | + |
| ➤ Antiangiogene Therapie (z.B. bei Angiosarkom) | 4 | C | +/- |
| ➤ Trabectedin (nach Anthrazyklin / Ifosfamid-Versagen bei Leiomyosarkomen) | 2b | B | + |

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Brustkrebs Nachsorge

Brustkrebs Nachsorge

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- **Versionen 2002–2015:**
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Böhme / Costa / Diel / Gerber / Hanf /
Heinrich / Janni / Kaufmann / Kümmel /
Lux / Maass / Möbus / Mundhenke /
Oberhoff / Rody / Scharl / Solomayer /
Thomssen**
- **Version 2016:**
Huober / Diel

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 asymptomatischer 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,
sexuelle Beschwerden, kognitive Einschränkungen | 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**
Schwangerschaft, Kontrazeption,
Sexualität, Lebensqualität, Meno-
pausensyndrom, Angst vor Rezidiv
- **Zweitmeinung zur Primärtherapie**
- **Allgemeine Beratung (z.B. Genetik,
HRT, prophylaktische Operationen,
Brustrekonstruktion)**

4 C +

2c B ++

2c C +

Brustkrebs Nachsorge Ziele

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

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- | | | | |
|---|-----------|----------|-----------|
| ➤ 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 g/d | 2b | B | + |
| ➤ Moderate Sportintervention bei Bewegungsmangel | 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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Routine-Nachsorgeuntersuchungen bei asymptomatischen Patientinnen

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Untersuchungen:

- **Anamnese (spezifische Symptome)**
- **Untersuchung**
- **Brust-Selbst-Untersuchung**
- **Mammographie**
- **Mammasonographie**
- **Mamma-MR in der Routine**
- **Mamma-MR bei unklarer Mammo-
graphie / -sonographie**
- **Gynäkologische Untersuchung**
- **DXA-Scan zu Therapiebeginn und
risikoadaptiert in regelmäßigen Abständen
bei Frauen mit frühzeitiger Menopause
und Frauen unter AI Therapie**

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1a	A	++
1a	B	++
5	D	+
1a	A	++
2a	B	++
3b	B	+/-
3b	B	+
5	D	++
5	D	+

Routine-Nachsorgeuntersuchungen bei asymptomatischen Patientinnen

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

Früherkennung von potenziell heilbaren Erkrankungen

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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
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Kontralaterales Mammakarzinom:

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

Früherkennung von potenziell heilbaren Erkrankungen

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Sonstige Zweitkarzinome:

Kolorektal RR 3,0; Endometrium RR 1,6
Ovar RR ca. 1,5; Lymphome RR 7

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

Brustkrebs Nachsorge Synopsis

Empfehlung für asymptomatische Patientinnen

(mod. nach ASCO-ACS Empfehlungen 2016, NCCN 1.2016 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.
Selbstuntersuchung		monatlich					
Bildgebende Diagnostik, Laboruntersuchungen		indiziert nur bei Symptomatik +/- Befunden +/- Verdacht auf Rezidiv/Metastasen					
Mammo-graphie und Sono-graphie	BET**	ipsilat.: alle 12 Mon. kontralat.: alle 12 Mon.			beidseits: alle 12 Monate		
	Mastektomie	kontralateral alle 12 Monate					

* Fortlaufende "Nachsorgeuntersuchungen" bei noch laufender adjuvanter Therapie

** nach BET: Erste Mammographie 1 Jahr nach initialer Mammographie, oder zumindest 6 Monate nach abgeschlossener 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 +/-*

*Studien empfohlen

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

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

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Loko-regionäres Rezidiv

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Loko-regionäres Rezidiv

- **Version 2002:**
Brunnert / Simon
- **Versions 2003–2015:**
**Audretsch / Bauerfeind / Costa /
Dall / Fehm / Fersis / Friedrich / Harbeck /
Gerber / Göhring / Hanf / Lisboa / Maass /
Mundhenke / Rezai / Solomayer / Souchon /
Thomssen**
- **Version 2016:**
Rezai / Budach / Wenz

Loko-regionäres Rezidiv Inzidenz und Prognose

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Lokalisation	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 Lokalisationen²	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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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 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

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Risikofaktoren beim Lokalrezidiv für das Auftreten eines Re-Rezidivs

Oxford / AGO LoE / GR

➤ 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 / ER neg / positive 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)**
- **Re-BEO mit tumorfreien Rändern**
± Lappen-Rekonstruktion
 - Überlebensnachteil kann nicht ausgeschlossen werden
 - Schlechtes kosmetisches Resultat
 - Verschlechterte lokale Tumorkontrolle
- **Axilläre Intervention nach primärer AxDiss, falls cN0**
- **SNL nach prim. SNL falls cN0***
- **Palliative Operation in der M1-Situation**
(z.B. Schmerz, Ulzeration, psychosoziale Indikation)

3b B ++

3 C +/-

4 C -

1b B +/-

5 D +

*** Falls kein Sentinel identifiziert wird, sollte keine Axilladisektion erfolgen; keine Operation außerhalb der ipsilateralen Axilla wird empfohlen.**

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Operative Therapie

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

Lokoregionäres Rezidiv nach R0-Resektion – Systemische Therapie

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

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LoE / GR

- | | | | |
|---|-----------|----------|-----------|
| ➤ Endokrine Therapie bei endokrin
responsiblen Tumoren | 2b | B | ++ |
| ➤ Chemotherapie (ggfs. neoadjuvant) | 2b | B | + |
| ➤ Bei HER2-überexprimierenden
Tumoren | | | |
| 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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LoE/GR

Nach Re-BEO

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

3b C ++

3b C +/-

Nach Mastektomie

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

2b B +/-

3b C -

Thoraxwandrezidiv nach Mastektomie

Axilläres Rezidiv – Lokale Behandlung

Oxford AGO
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

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

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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Endokrine und zielgerichtete Therapie des metastasierten Mammakarzinoms

Endokrine Therapie des metastasierten Mammakarzinoms

- **Version 2002:**
Gerber / Friedrichs
- **Versionen 2003–2015:**
**Albert / Bischoff / Dall / Fersis / Friedrich /
Gerber / Huober / Janni / Jonat /
Kaufmann / Liedtke / Loibl / Lück / von
Minckwitz / Möbus / Müller / Mundhenke /
Nitz / Schneeweiß / Schütz / Stickeler**
- **Version 2016:**
Hanf / Mundhenke

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%) für ER
- 33% (95%CI 29-38%) für PR
- 8% (95% CI 6-10%) für HER2

Wechsel der Rezeptorexpression von positiv zu negativ und von negativ zu positiv

- 4% and 14% für ER
- 46% and 15% für PR
- 13% and 5% für HER2

Endokrine Therapie

Allgemeine Überlegungen

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Therapieentscheidungen aller Behandlungslinien sollten die Vortherapien, Alter und Komorbiditäten sowie den jeweiligen Zulassungsstatus berücksichtigen.

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(nalogon) + Fulvestrant	1b	B	+
➤ GnRH-A.+ Fulvestrant + Palbociclib	1b	B	+
➤ Aromataseinhibitoren ohne OFS	3	D	--

Endokrine Therapie

der postmenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom

***Keine Hinweise für die Überlegenheit eines einzelnen Aromataseninhibitors.**

Um eine spätere Therapie nach Zulassungsstatus mit Everolimus zu ermöglichen, sollte in der Erstlinientherapie bevorzugt ein nicht-steroidaler AI eingesetzt werden. MA[§]: Megestrol-Acetat

**Oxford / AGO
LoE / GR**

➤ Fulvestrant 500 mg	1b	B	++
➤ Aromatase inhibitor (dritte Generation) **	1a	A	++
➤ Tamoxifen	1a	A	++
➤ Letrozol + Palbociclib	1b	B	+
➤ Fulvestrant 500 mg plus Palbociclib	1b	B	+
➤ Exemestan + Everolimus	1b	A	+
➤ Tamoxifen + Everolimus	2b	B	+
➤ MPA/MA[§]	1a	A	+/-
➤ Fulvestrant 250 mg + Anastrozol	1b	B	+/-
➤ Estradiol Valerat 2-6 mg täglich	2b	C	+/-
➤ Frühere Behandlungslinien wiederholen	5	D	+/-

Therapiealgorithmen nach adjuvanter Tamoxifentherapie

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**Fulvestrant 500 oder
Nicht-steroidaler AI der
3. Generation oder Tamoxifen***

**Exemestan +
Everolimus**

**Fulvestrant 500 mg
+/- Palbociclib**

Tamoxifen

**Fulvestrant 500 mg
+/- Palbociclib**

**Exemestan +
Everolimus**

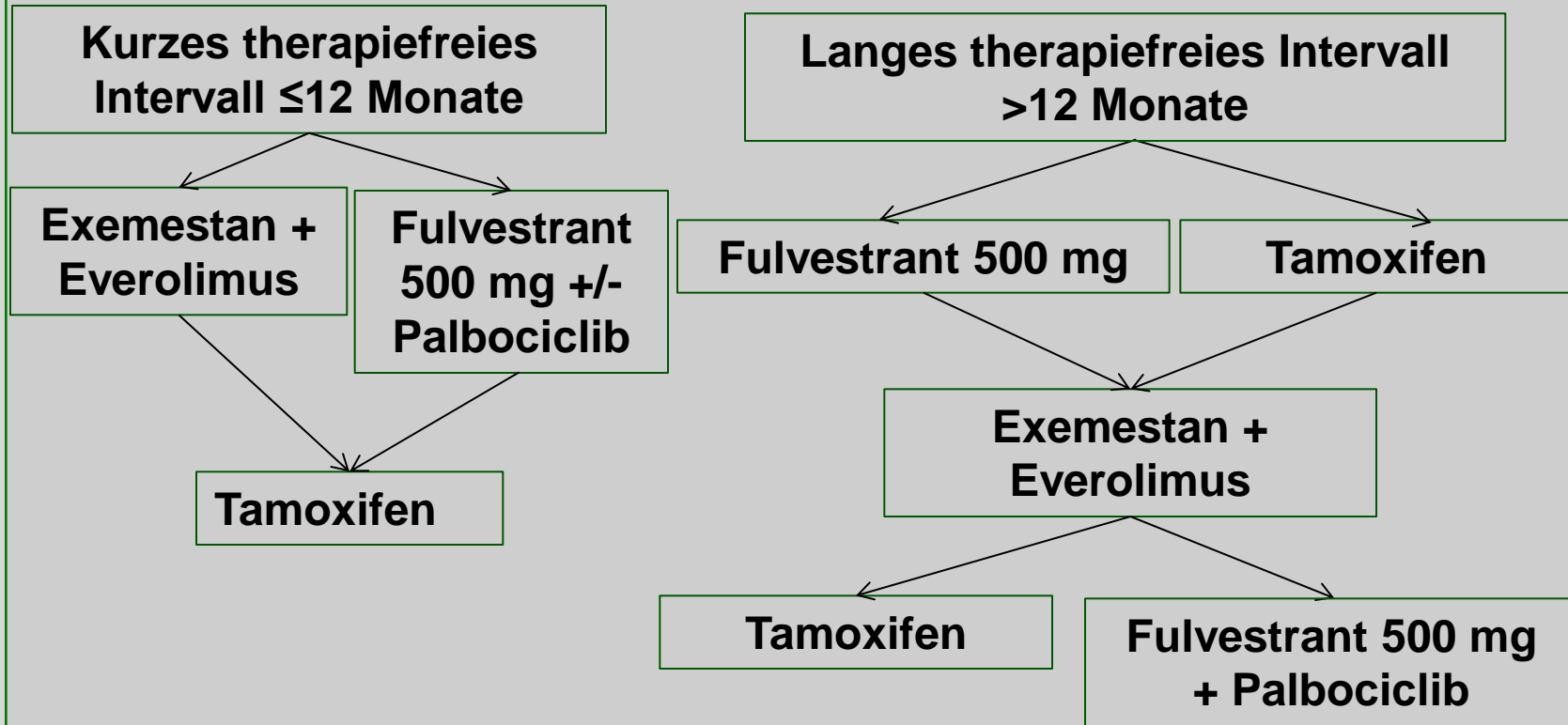
Tamoxifen

*(nach langem Therapie-freiem Intervall)

Therapiealgorithmen nach adjuvanter AI Therapie

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Endokrine Therapie der postmenopausalen Patientin mit HER2-negativem metastasiertem Mamma- karzinom 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 B +

1b B -

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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 Mammakarzinompatientin

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LoE / GR**

➤ Anastrozol und Trastuzumab	1b	B	+/-
➤ Letrozol und Trastuzumab	2b	B	+/-
➤ Letrozol und Lapatinib	1b	B	+/-
➤ Fulvestrant und Lapatinib	1b	B	+/-

Geringe Wirksamkeit einer alleinigen endokrinen Therapie.

Eine Induktions-Chemotherapie zusammen mit einer anti-HER2-Therapie (gefolgt von endokriner plus anti-HER2-Erhaltungstherapie) 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 bestätigtem Rezeptorstatus)	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%	Keine Auskunft
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-) p: 0,25 5.9 vs. 3.3 (HER2+) p: 0,53	(CR +PR) 20 vs. 9% p: 0,048	30 vs. 26.4 (alle), n.s.

Simultane oder sequenzielle endokrin-zytostatische Behandlung

Oxford / AGO
LoE / GR

➤ **Simultane endokrin-zytotoxische Therapie**

1b A -

- Höhere Ansprechraten und progressions-
freies ÜL möglich, keine Verbesserung des
Gesamtüberlebens
- Kann Nebenwirkungsrate/Toxizität erhöhen

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

2b B ++

- Verlängert das progressionsfreie Überleben

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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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 2003–2015:**
**Bischoff / Dall / Fersis / Friedrichs /
Harbeck / Jakisch / Janni / von Minckwitz /
Möbus / Müller / Rody / Scharl /
Schmutzler / Schneeweiss / Schütz /
Stickeler / Thomssen**
- **Version 2016:**
Thill / Rody

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**

Endokrine Resistenz bei metastasiertem Mammakarziom

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Primäre endokrine Resistenz:

Rezidiv während der ersten zwei Jahre einer adjuvanten endokrinen Therapie (ET) oder innerhalb der ersten 6 Monate einer endokrinen First-line Therapie beim metastasierten Mammakarzinom während laufender ET

Sekundäre endokrine Resistenz:

Rezidiv während einer adjuvanten ET, aber erst nach den ersten 2 Jahren oder innerhalb 12 Monate nach abgeschlossener adjuvanter ET oder eine Progression \geq 6 Monate nach Initiierung einer ET in der metastasierten Situation während laufender ET

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

Taxane-containing Regimens for Metastatic Breast Cancer

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Gherzi D, Willson ML, Chan MM, Simes J, Donoghue E, Wilcken N. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2015 Jun 10;6:CD003366.

See: Forest plot of comparison: I Overall survival, outcome: I.I Overall effect: Taxane-containing regimes vs. not

mBC HER2-negativ / HR-positiv

Palliative Chemotherapie

nach Anthrazyklin-Vorbehandlung*

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➤ 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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	Oxford / AGO LoE / GR		
			++
➤ Experimentelle Therapien in Studien			
➤ Capecitabin	2b	B	++
➤ Eribulin	1b	B	++
➤ Vinorelbin	2b	B	++
➤ (Peg)-liposomales Doxorubicin	2b	B	+
➤ Taxan Re-Challenge	2b	B	+
➤ Anthrazyklin Re-Challenge	3b	C	+
➤ Metronomische Therapie (z.B. Cyclophos. und MTX)	2b	B	+
➤ Gemcitabin + Cisplatin / Carboplatin	2b	B	+/-
➤ Gemcitabin + Capecitabin	2b	B	+/-
➤ Gemcitabin + Vinorelbin*	1b	B	-

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** 1b B +

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Bevacizumab beim HER2-neg. metastasierten Mammakarzinom

Oxford / AGO LoE / GR

➤ 1st line in Kombination mit:

➤ Paclitaxel (wöchentlich)	1b	B	+
➤ Capecitabine	2b	B	+
➤ Anthracyklinen	2b	B	+/-
➤ Nab-Paclitaxel	2b	B	+/-
➤ Docetaxel (dreiwöchentlich)	1b	B	+/-

➤ Cap+Bev als Erhaltung nach Doc + Bev

1b B +/-

➤ 2nd line als Behandlung durch multiple Linien

1b B +/-

➤ 2nd line in Kombination mit:

➤ Taxanen	1b	B	+/-
➤ Capecitabine	1b	B	+/-
➤ Gemcitabine oder Vinorelbine	1b	B	-

Erstlinientherapie beim HER2-pos. metastasierten Mammakarzinom

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	Oxford / AGO LoE / GR		
➤ Docetaxel + Trastuzumab + Pertuzumab	1b	A	++
➤ Paclitaxel (wk) + Trastuzumab + Pertuzumab	2b	B	+
➤ Vinorelbine + Trastuzumab + Pertuzumab	3b ^a	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	B	+/-
➤ Taxanes + Trastuzumab + everolimus	1b	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 „Endokrine +/- targeted Therapie“

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

➤ Vinorelbine + Lapatinib

➤ Trastuzumab + Lapatinib (HR neg. Pat.)

➤ Chemotherapie + Trastuzumab + („treatment beyond progression“)

- Trastuzumab + Pertuzumab
- Vinorelbine + Trastuzumab + Everolimus
(Trastuzumab resistent, Taxan vorbehandelt)

Oxford / AGO LoE / GR

1b A ++

1b B +

2b 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 Vor- behandlung, Therapie gemäß obenstehender Empfehlungen

5 D

Lapatinib beim HER2-positiven metastasierten Mammakarzinom

**Oxford / AGO
LoE / GR**

In Kombination mit

- **Trastuzumab für schwer vorbehandelte Patientinnen**
- **Paclitaxel als 1st line**
- **Capecitabine als > 2nd line**
- **Vinorelbine**
- **AI bei ER positiver Erkrankung**

2b B +

2b B -

1b B +

2b B +/-

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;...)

*Studienteilnahme empfohlen

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

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START

Osteoonkologie und Knochengesundheit

Osteoonkologie und Knochengesundheit

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Fehm / Fersis / Friedrich/ Friedrichs /
Hanf / Huober / Jackisch / Janni / Lux /
Maas / Nitz / Oberhoff / Schaller / Scharl /
Schütz / Seegenschmiedt / Solomayer /
Souchon**
- **Version 2016:**
Fehm / Solomayer

Bisphosphonate beim metastasiertem Mammakarzinom

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	Oxford / AGO LoE / GR		
➤ Hyperkalzämie	1a	A	++
➤ Reduktion skelettaler Komplikationen	1a	A	++
➤ Reduktion von Knochenschmerzen	1a	A	++
➤ Verlängerung der Zeit bis zum Auftreten von Knochenschmerzen	1a	A	++
➤ Therapie nach ossärer Progression	5	D	++

Denosumab beim metastasierten 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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**FORSCHEN
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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	++
➤	Zoledronate i.v. 4 mg q12w*	1a	A	+
➤	Denosumab 120 mg s.c. q4w	1a	A	++
➤	Denosumab 120 mg s.c. q 12w	4	C	-
➤	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

➤ Mit Frakturrisiko

**Oxford / AGO
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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 +/-

➤ Reduktion der Strahlentherapie induzierten

1b B +

Schmerzzunahme mit Dexamethason

Nur wenige Studien mit Mammakarzinompatientinnen!

Knochenmetastasen

Schmerztherapie nach Vorbestrahlung

**Oxford / AGO
LoE / GR**

Rekurrenter Knochenschmerz in vor- bestrahlten Arealen des Skeletts

➤ Einmalige RT *	3b	C	++
➤ Fraktionierte RT *	3b	C	+
➤ Radionuklidtherapie	3b	C	+
➤ MR-gesteuerter hochfokussierter Ultraschall	1b	B	+
➤ Radiofrequenzablation	4	C	+
➤ Kryoablation	4	C	+

* 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 osteoprotektive Therapie 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 +/-

➤ Denosumab (60 mg s.c. q6mo)

- Postmenopausale Patientinnen

1b^a B +/-

Dosierung adjuvanter Bisphosphonate zur Verbesserung des Überlebens

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- **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)**

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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
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1b	B	++
1b	A	+

- **Denosumab**
 - Therapie
 - Prävention

1b	B	++
1b	A	+

- **HRT**

5	D	-
---	---	---

- **Bestimmung der Knochendichte vor Therapie
mit AI oder bei vorzeitiger Menopause**

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

- **Risikoadaptierte Kontrolle der Knochendichte
im Verlauf**

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

Therapie und Prävention des Tumorthherapie induzierten Knochenmasseverlusts / Osteoporose

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

- Sportl. / körperl. Aktivität
- Vermeidung von Immobilisation
- Kalzium (1000–1.500 mg/d)**
- Vit. D3 (800–2000 U/d)
- Nikotinverzicht, nur mäßiger Alkoholkonsum
- Vermeidung eines BMI < 20 kg/m²
- Substanzen, die zur Therapie einer Osteoporose zugelassen sind (s. folgende Vorlage)

Oxford / AGO LoE / GR

4	C	++
4	C	++
4	C	++
4	C	++
2b	B	++
3b	C	++

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

- **Version 2002:**
Dall / Fersis / Friedrich
- **Versionen 2003–2015:**
Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Fehm / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon
- **Version 2016:**
Lux / Schütz

Besondere Metastasenlokalisationen

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- **Leber- und Lungemetastasen**
- **Maligne Pleura- und Perikardergüsse**
- **Aszites**
- **Knochenmarkinfiltration**
- **Weichteilmetastasen**
- **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 nur bei gutem Therapieansprechen der systemischen Therapie	2b	C	+
➤ Option bei Patientinnen in gutem Zustand mit spät aufgetretener Oligometastasierung	3a	B	+
➤ Lokale Behandlung bei Schmerzen, Exulzation, Ileus, persistierender(n) 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

Lokale Therapie in der primär metastasierten Situation

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Oxford / AGO
LoE / GR

➤ Lokale Therapie (R0) des Primärtumors	1b	B	+/-
➤ Axillaoperation bei cN1	5	C	+/-
➤ Sentinel in cN0	5	C	-
➤ Lokale Radiotherapie des Primärtumors			
➤ Alleine	3a	C	+/-
➤ Nach lokaler Operation mit brusterhaltender Therapie oder Mastektomie und entsprechender Indikation	3a	C	+

Hepatische Metastasen

Lokale Therapie

Oxford / AGO
LoE / GR

➤ Operative Resektion (R0)

3a B +/-

HR positiv: Chemotherapie-sensibel, langes DFS,
keine extrahepatischen Metastasen, ≤ 3 Metastasen

HER2 positiv: Alter < 50 Jahre, Metastase < 5 cm,
keine weiteren Metastasen

➤ Regionale Chemotherapie

3b C +/-

➤ Regionale Radiotherapie

4 C +/-

(SIRT, stereotaktische Radiotherapie mittels
SRS-VMAT, Radiochemoembolisation, andere
Bestrahlungsverfahren)

➤ Thermoablation

3b C +/-

(RFA, LITT, Kryotherapie)

Pulmonale Metastasen

Lokale Therapie

Oxford / AGO

LoE / GR

- **Vor einer Operation: Staging und Biopsie (CT- gesteuerte Feinnadelaspiration oder transbronchiale Biopsie)**
- **Resektion mittels VATS oder konventionell**
 - Im Falle multilokulärer metastasischer Erkrankung
 - Im Falle einzelner Metastasen einer Lokalisation und mit kurativer Intention
- **Thermoablation (CT-gesteuert RFA, LITT)**
- **Regionale Radiotherapie**
(z.B. stereotaktische Radiotherapie mittels SRS-VMAT)

3a B +

3a B -

3a B +/-

3b C +/-

4 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 [Dyspnoe (80%), Thoraxwandschmerz (30%), nicht produktiver Husten (10%)]
- Das Überleben ist assoziiert mit weiteren Metastasenlokalisationen, ECOG PS, Alter und Ausdehnung der Pleura-Metastasierung.

Diagnostik:

- Klinische Untersuchung
- Röntgen, Ultraschall, CT
- Histologischer / Zytologischer Nachweis durch Punktion oder Thorakoskopie (→ 50% falsch negativ).

Maligner Pleuraerguss

Lokale Therapie

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LoE / GR

- Wenn die erwartete Lebenszeit kurz ist, sollten weniger invasive Prozeduren in Betracht gezogen werden
- VATS und Talkum-Pleurodese*
- Medikamentöse Pleurodese*
 - Talkumpulver
 - Bleomycin, Doxycyclin, Mitoxantron
 - Povidon-Jodid (20 ml 10% Lösung)
- Kontinuierliche Pleuradrainage
- Systemtherapie nach Pleurodese
- Lokale Antikörpertherapie (z.B. Catumaxomab)
- Wiederholte Pleurapunktionen

4 C ++

1b B ++

1a B +

2b C +/-

1b B +

2a B +

3b C +/-

3b C -

4 C +/-

* Adäquate Schmerztherapie

VATS = video-assisted thorac. surgery

Maligner Aszites

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**Oxford / AGO
LoE / GR**

Aszites:

- | | | | |
|---|-----------|----------|------------|
| ➤ Punktion, Drainage bei Symptomen | 4 | D | ++ |
| ➤ Lokale Chemotherapie | 3b | D | +/- |
| ➤ Systemische Therapie | 3b | D | ++ |
| ➤ Lokale Antikörpertherapie (z.B. Catumaxomab) | 3b | D | +/- |

Maligner Perikarderguss

Lokale Therapie

**Oxford / AGO
LoE / GR**

Symptomatischer Perikarderguss:

- Drainage, chirurgische Fensterung des Perikards
- Thorakoskopie (VATS)
- Ultraschall geführte Punktion und Instillation von Mitoxantron, Cisplatin

3b B ++

4 D +

4 D +/-

Knochenmarkinfiltration (mit Panzytopenie)

Oxford / AGO
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

Operation im Falle lokoregional limitierter metastatischer Erkrankung (Haut, Muskel, Lymphknoten) mit Komplettresektion (R0) und keine weiteren Metastasen nach Staging

4 C +

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 2003–2015:**
**Bischoff / Diel / Friedrich / Gerber /
Huober / Lück / Maass / Müller / Nitz /
Jackisch / Jonat / Junkermann / Rody /
Schütz**

- **Version 2016:**
Loibl / Müller

Unter Mitarbeit von:

Petra Feyer und Dirk Rades (DEGRO)

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.

Background OS-Score (Rades et al.)

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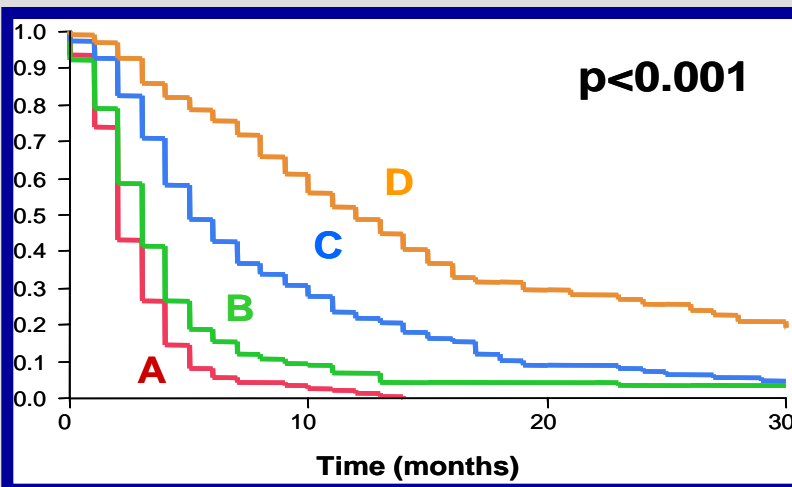
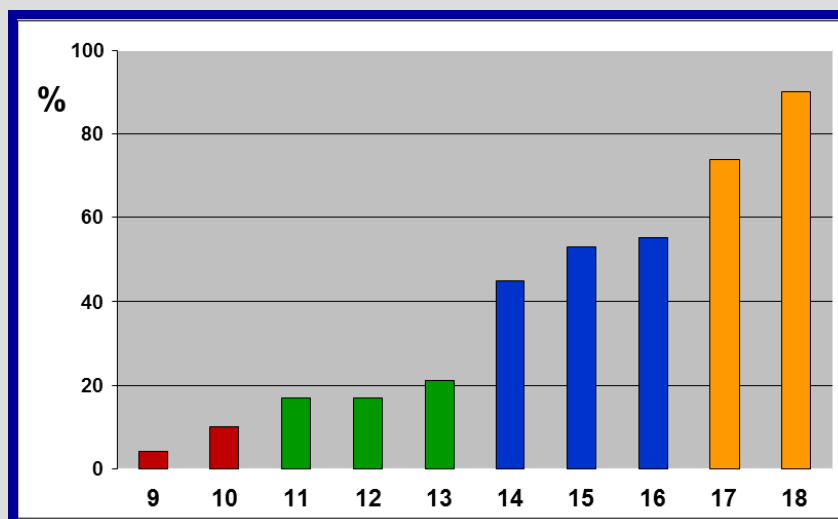
- Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed.
- This score was based on the four independent prognostic factors that were significantly associated with survival on multivariate analysis: age, performance status, extracranial metastases at the time of WBRT, and interval between tumor diagnosis and WBRT.
- The score for each prognostic factor was determined by dividing the 6-month survival rate (in %) by 10.
- The total score for each patient represented the sum of the scores for each prognostic factor.
- Total scores ranged from 9 to 18 points, and patients were divided into four groups.

WBRT: Survival Score (N=1,085)

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	Überleben nach 6 Monaten (%)	Score
Alter		
≤ 60 Jahre	43	4
≥ 61 Jahre	25	3
Karnofsky-Index		
< 70	8	1
≥ 70	53	5
Extrakranielle Metastasen		
Nein	51	5
Ja	24	2
Intervall von Erstdiagnose bis GHRT		
≤ 8 Monate	32	3
> 8 Monate	36	4



**Der Score wurde bereits
validiert
(350 neue Patienten).**

Rades et al., STO 2008
Dziggel et al., STO 2013

Singuläre / solitäre Hirnmetastase

Oxford/AGO

LoE / GR

Alleinige Lokaltherapie: SRS ($\leq 4\text{cm}$) o. FSRT o. Resektion

2b B ++

WBRT + Boost (SRS, FSRT) o. Resektion + WBRT

2a B ++

Resektion + Bestrahlung des Tumorbetts (ohne WBRT)

2b B +

Alleinige WBRT*

2b B +

- WBRT zusätzlich zu SRS/FSRT oder Resektion verbessert die lokale Kontrolle und Symptomkontrolle, nicht aber das Überleben. Gleichzeitig scheint bei zusätzlicher WBRT eine größere neurokognitive Beeinträchtigung aufzutreten.
- Im Falle einer neurochirurgischen Resektion sollte eine Nachbestrahlung des Tumorbetts (alleinige lokale RT oder Boost bei WBRT) erfolgen. Eine Resektion bietet vermutlich keinen generellen Vorteil gegenüber einer Strahlentherapie. Indikationen zur Resektion siehe Hintergrunddia.

* Patientinnen mit ungünstiger Prognose und/oder schlechtem Allg.zustand

SRS = stereotactic radiosurgery (einzeitig)

FSRT = fractionated stereotactic RT

WBRT = whole brain radiotherapy

2-3 (2-4) Hirnmetastasen (Oligo-)

**Oxford/AGO
LoE / GR**

**Alleinige Lokaltherapie: SRS ($\leq 4\text{cm}$) oder FSRT
WBRT + Boost (SRS, FSRT)**

2b B ++

2a B ++

Alleinige WBRT**

2b B +

- **WBRT zusätzlich zu SRS/FSRT verbessert die lokale Kontrolle und Symptomkontrolle, nicht aber das Überleben. Gleichzeitig scheint bei zusätzlicher WBRT eine größere neurokognitive Beeinträchtigung aufzutreten.**

*** Bei Patientinnen mit ungünstiger Prognose und / oder schlechtem Allgemeinzustand**

SRS = stereotactic radiosurgery (einzeitig)

FSRT = fractionated stereotactic RT

WBRT = whole brain radiotherapy

NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases

Study design:

Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.

Conclusion:

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

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.

Mögliche Entscheidungsfaktoren Neurochirurgie vs. stereotaktische Strahlentherapie

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Pro Neurochirurgie:

- Histologische Sicherung nach z.B. langem rezidivfreiem Intervall
- Sofortige Dekompression notwendig, lebensbedrohliche Symptome
- Stereotaktische RT aufgrund der Tumorgröße nicht möglich

Pro primäre Radiotherapie:

- Tumorlokalisation nicht geeignet für chirurgische Resektion
- Mehr als 4 Läsionen

Multiple Hirnmetastasen > 3 (4) Läsionen

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- **WBRT (supportiv Steroide*)**
- **Hippocampusschonung**
- **Radiochemotherapie zur Kontrolle intrazerebral**
- **Chemotherapie allein**
- **Corticosteroide allein***

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

*Symptomadaptiert

Systemische und symptomatische Therapie von Hirnmetastasen

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- **Fortsetzung der anti-HER2-Therapie**
- **Lapatinib + Capecitabin als initiale Behandlung (HER2 pos. Fälle)**
- **Chemotherapie als alleinige Primärbehandlung**
- **Antikonvulsiva nur bei Anfallssymptomatik**
- **Glucocorticoide nur wenn Symptome und / oder Verdrängungseffekt**

**Oxford / AGO
LoE / GR**

2c	C	+
1b	B	+/-
3	D	-
3	C	+
3	C	++

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

FORSCHEN
LEHREN
HEILEN

Komplementäre Therapien

Hormontherapie

„Survivorship“ (Rezidiv-Prävention)

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- **Versionen 2002–2015:**
**Albert / Bauerfeind / Blohmer / Fersis /
Friedrich / Gerber / Göhring / Hanf / Janni /
Kümmel / von Minckwitz / Oberhoff / Scharl /
Schmidt / Schütz / Thomssen**

- **Version 2016:**
Kümmel / Schmidt

„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 --
- **Unter Systemtherapie: Besondere Beachtung gilt möglichen
Medikamenteninteraktionen**

Komplementäre Therapien prä- und postoperativ

Oxford
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Präoperativ:

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

1b B +

Postoperativ:

- **Akupunktur** (bei Schmerzen, Ängstlichkeit, Muskelbeschwerden)

2b B +/-

- **Akupunktur** (bei Übelkeit, Erbrechen)

2b B +

- **Massage Therapie** (bei Schmerzen)

2b C +/-

- **Frühzeitige Bewegungstherapie postop.**
beugt Dysfunktion der oberen Extremität vor
CAVE: vermehrt Wundsekret

1a A +

- **Prophylaktische Lymphdrainage**

1b B -

Komplementäre Therapien

Behandlungsphase - Einfluss auf Toxizität I

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

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LoE / GR**

- **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** (evtl. Besserung der Fatigue,
Beachte: inhibiert P Enzyme, z.B. CYP3A4)
- **L-Carnitin** (Prävention der Toxizität, Verbesserung
periphere Neuropathie)
- **L-Carnitin** (keine Verbesserung der Fatigue)
- **Curcumin** (Zusatz, um Radiodermatitis zu vermindern)
- **Ingwer** (Chemotherapie induzierte Übelkeit/Erbrechen;
cave: Wechselwirkungen)

1a B +/-

2a B +/-

2b C -

2b C -

1b B --

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 Kräutermedizin

zur Behandlung chemotherapiebedingter Nebenwirkungen

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

1b B -

➤ Homöopathische Medizin

gegen therapiebedingte Nebenwirkungen

1b B +/-

➤ Topische Calendula (>=20% Calendulaanteil) zur Prophylaxe einer akuten Dermatitis unter Strahlentherapie

➤ Traumeel S® Mundspülung bei chemotherapieinduzierter Stomatitis

➤ Topische Anwendung Silymarin (Mariendisteleextrakt)

3a B +/-

➤ Akupunktur zur Verbesserung von:

➤ Chemotherapie-induzierte Übelkeit, Erbrechen

1a B +

➤ Kognitive Dysfunktion

5 D +/-

➤ Fatigue

1a B +

➤ Schmerzen

1a B +/-

➤ Leukopenie (Moxibustion)

2b B +/-

➤ Chemotherapie-induzierter Polyneuropathie

2b^a 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

Oxford AGO
LoE / GR

- | | | | |
|--|-----------|----------|-----------|
| ➤ Anstreben eines normalen BMI/
Abnehmen bei Übergewicht, unabhängig
vom HR Status (verbessert Prognose-DFS/OS) | 1a | A | ++ |
| ➤ Ernährung mit geringem Fettanteil
(verbessert Prognose – DFS/OS,
Ernährungsberatung empfohlen) | 1a | A | + |
| ➤ Vermeidung stark fetthaltiger Diätprodukte | 2b | C | + |
| ➤ Lignan-/Ballaststoff-haltige Lebensmittel
(u.a. Saaten z.B. Leinsamen) | 2a | B | + |
| ➤ Beachten genereller Ernährungs-
empfehlungen (z.B. von DGE, WCRF) | 2a | B | ++ |
| ➤ Diät-Extreme
(are associated with less favourable outcomes) | 1b | B | -- |

Komplementäre Therapien

Rezidiv-Prävention III

Pflanzliche Therapieansätze - Nahrungsergänzung

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	Oxford	AGO
	LoE / GR	
➤ 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 B	+/-
➤ 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 | 1a | B | +/- |
| ➤ 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

Gynäkologische Probleme bei Mammakarzinompatientinnen

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➤ Version 2015:

Loibl / Gerber

(unter Mitarbeit von Hanf / Kümmel und Stickeler / Scharl)

Version 2016:

Albert / Bauerfeind / Fersis / Thill

Hormon-(Ersatz-)Therapie (HT) für Östrogenmangelsymptome nach Mammakarzinom-Diagnose und -Therapie

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	Oxford LoE / GR	AGO
➤ 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		
➤ Östriol (E3 0,03 mg)	4 D	+/-
➤ Östradiol (E2) während einer AI-Therapie	4 C	-

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) | 1a | 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 | - |
| ➤ Melatonin (verbesserte Schlafqualität) | 2b | C | + |

CAM-Therapie

Postmenopausale Symptome II

Bei laufender onkologischer Standardtherapie:
CAVE Medikamenten-Interaktionen!

➤ Soja— Isoflavonoide

Hitzewallungen

Schlafstörungen

topische vaginale Applikation

➤ Rotklee— Isoflavonoide

Hitzewallungen und Schlafstörungen

(Aktivierung von MaCa-Zellen insbes. bei hormon-rezeptorpositiver Erkrankung nicht ausgeschlossen)

➤ Leinsamen (40g/d) (bei HR+ ≤ 10g/d (1 Essl.))

➤ Traubensilberkerze gegen Hitzewallungen

Traubensilberkerze und Johanniskraut als fixe Kombi

➤ Johanniskraut-Produkte (in Kombinationstherapie)

(pharmakologische Interferenz mit endokriner Therapie, Zytostatika und Tyrosinkinase-Inhibitoren)

➤ Ginseng Wurzel (Panax ginseng or P. quinquefolius)

➤ Bromelain + Papain + Selen + Lektin (AI-induzierten Gelenkbeschwerden)

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1b B -

1b B +/-

1b B +/-

1b B +/-

2b B +/-

1b B -

1b B +/-

1b B - -

1b B -

3b B +

Postmenopausale Symptome III

Komplementäre Therapien

Oxford / AGO
LoE / GR

Allgemeine Ansätze:

➤ **Körperliches Training / Sport**

1b B ++

➤ **Mind Body-Medizin**

1b B +

(Yoga, Hypnose, Schulung, Beratung)

➤ **Kognitive Verhaltenstherapie**

1b B ++

➤ **Akupunktur**

Aromatase-Inhibitor induzierte Arthralgie

2b B +

Hitzewallung

1b B +

Depression

2b B +/-

Angst, Schlafstörungen

3b C +/-

(Keine Akupunktur in Tumorregion mögliche Zellstreuung)

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

Oxford / AGO
LoE / GR

➤ Erhaltung der Ovarialfunktion

➤ CHT + GnRHa

1a B +/-

(GnRHa Applikation > 2 Wochen vor Chemotherapie)

Beeinflussung des Chemoeffektes nicht sicher ausgeschlossen!

➤ Beratung über Fertilitätserhaltung

4 C +

➤ Fertilitätserhalt mit assist. reprod. Therapie

(Information: www.fertiprotect.de)

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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Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

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Author (year of publication)	Odds Ratio	95%CI	Treated Events	Controls Events
Li M (2008)	0.31	0.11-0.89	8/31	17/32
Badaway (2009)	0.06	0.02-0.20	4/39	26/39
Sverrisdottir 1 (2009)	0.19	0.04-1.06	14/22	18/20
Sverrisdottir 2 (2009)	2.03	0.31-13.27	27/29	20/23
Del Mastro (2011)	0.27	0.14-0.54	13/148	35/133
Gerber (2011)	0.56	0.19-1.62	9/30	13/30
Sun (2011)	0.38	0.06-2.30	3/11	5/10
Munster (2012)	1.09	0.22-5.52	4/26	3/21
Elgindy 1 (2013)	0.76	0.18-3.25	4/25	5/25
Elgindy 2 (2013)	1.0	0.25-4.00	5/25	5/25
Song (2013)	0.50	0.25-1.03	15/89	27/94
Karimi-zarchi (2014)	0.05	0.01-0.29	2/21	14/21
Li JW (2014)	0.44	0.04-4.35	1/54	3/73
Moore (2015)	0.30	0.10-0.87	5/66	15/69
Summary: Fixed effect	0.34	0.25-0.46	114/616	206/615
Summary: Random effect	0.36	0.23-0.57		

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Testung der ovariellen Reserve

**Oxford / AGO
LoE / GR**

**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

Oxford / AGO
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➤ Barriere-Methoden	5	D	+
➤ Sterilisation (Tubenligatur / Vasektomie)	5	D	+
➤ Nicht-hormonelle intrauterine devices (IUDs)	3b	D	+
➤ Levonorgestrel-releasing IUDs	2b	C	-
➤ Entfernung bei Erstdiagnose	4	D	+/-
➤ Timing-Methoden	5	D	-
➤ Ausschließl. Progesteron-Kontrazeptiva (oral / im)	5	D	-
➤ Komb. orale Kontrazeptiva	5	D	-

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Kontrazeptive Notfall-Optionen für Frauen nach Brustkrebs

Oxford / AGO
LoE / GR

➤ **Copper intrauterine devices (Cu-IUD)**

5 D +

➤ **Levonorgestrel, Ulipristal**

5 D +

Sexuelle Gesundheit

Oxford / AGO
LoE / GR

- | | | | |
|---|----|---|---|
| ➤ Tests zu Faktoren sexueller Dysfunktion | 5 | C | + |
| ➤ Nutzung von Patientinnenfragebögen | 4 | C | + |
| ➤ Vaginale Trockenheit
Nicht-hormonelle Gleitmittel /Moisturizer | 1b | B | + |
| ➤ Psychoedukative Unterstützung,
Gruppentherapie, Sexualberatung,
Eheberatung, Psychotherapie | 1b | B | + |

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Tests zur sexuellen Gesundheit

➤ **Sexual Complaints Screener (SCS) for women*** German Translation

Screening-Check-Fragebogen: Sexuelle Gesundheit

- 1 Sind Sie zufrieden mit Ihrem Sexualleben? Ja, nein, wenn nein
- 2 Seit wann/wie lange sind Sie mit Ihrem Sexualleben unzufrieden?
- 3 Ihr Problem im Sexualleben ist:
 - ① Kein Interesse bzw. keine Lust
 - ② Reduzierte Empfindlichkeit/Sensibilität im Genitalbereich
 - ③ Trockenheit der Scheide
 - ④ Problem, den Orgasmus zu erreichen
 - ⑤ Schmerzen beim Geschlechtsverkehr
 - ⑥ Andere
- 4 Welche Probleme stören Sie am meisten? 1, 2, 3, 4, 5, 6.
- 5 Wollen Sie über diese Probleme mit Ihrem Arzt/Ihrer Ärztin reden?

* Hatzichristou D, Rosen RC, Denogatis LR, Low WY, Sadovsky R, Symonds T. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-348

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