Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Herausgegeben von der Kommission Mamma
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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 ≥ 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"

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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**

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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

10+ LN	≥ 10 tumor infiltrated axillary lymph nodes
A	Doxorubicin
ABCSG-8	Austrian Breast- and Colorectal Cancer Study Group
AC	Doxorubicin / cyclophosphamide
ACR	American College of Radiology
AD	Doxorubicin / docetaxel
ADH	Atypical ductal hyperplasia
adj. A	Adjuvant doxorubicin
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie e.V.
AH	Atypical hyperplasia
AI, AIs	Aromatase inhibitor(s)
ALH	Atypical lobular hyperplasia
A_{lip}	Liposomal doxorubicin
ALND	Axillary lymph node dissection
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AP	Doxorubicin / paclitaxel
ARNO	Arimidex® versus Nolvadex® (trial on adjuvant therapy)
ASCO	American Society of Clinical Oncology
ATAC	Arimidex®, Tamoxifen Alone or in Combination Trial
autolog LADO	Autologous latissimus dorsi muscle flap
AxDiss	Axillary dissection
BC, bc	Breast cancer
Bc-spec	Breast cancer specific
BCS	Breast conserving surgery
BCSF	Breast cancer-free survival
BCT	Breast conserving therapy
BIG 1-98	Breast International Group
bilat.	Bilateral
Bip TRAM	Bi-pedicled TRAM
BMD	Bone mineral density
BMI	Body mass index
BR	Breast reconstruction
BRCA	Breast cancer
BS-BM	Basic score for brain metastases *(Viani GA et al. BMC Cancer. 2007;7:53)*

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Abbreviations – II

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/ *epirubicin 120* / 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
Cl	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

D	Docetaxel
D & C	Dilatation and curettage
D / Carbo	Docetaxel / carboplatin
DAC	Docetaxel / doxorubicin / cyclophosphamide
DARB	Darbepoetin
DC	Docetaxel / cyclophosphamide
DCIS	Ductal carcinoma in situ
dd	Dose-dense
DepoCyt®	Liposomal cytarabine, liposomal ara-C
DFI	Disease-free interval
DFS	Disease-free survival
DI	Dose intensity
DIEP-flap	Deep inferior epigastric perforator flap
Doc + Cap	Docetaxel + capecitabine
DOX, Doxo	Doxorubicin
E2, E_2	Estradiol
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EC	Epirubicin / cyclophosphamide
ECD	Extracellular-domain
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
ENT	Ear-nose-throat (otorhinolaryngologic)
EORTC	European Organization for Research and Treatment of Cancer
Epi	Epirubicin
EPO	Erythropoetin
ER	Estrogen receptor
ErbB2	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
ESF	Erythropoesis-stimulating factor
ETC	Epirubicin / paclitaxel / cyclophosphamide (dose-dense chemotherapy)
EWGBSP	European Working Group for Breast Screening Pathology

Abbreviations – IV

F	5-Fluorouracil
F/U, f.-up	Follow-up
FA 60 C	"US-FAC": 5-Fluorouracil / *doxorubicin 60* / 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", ("Bonneterre"): 5-fluorouracil / *epirubicin 100* / 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 Investigation en Cancer 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

Abbreviations – V

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
IHC	Immunohistochemistry
Inh.	Inhibitor
INT 0101	Intergroup study 0101
IR	Implant reconstruction
ITA	Italian Tamoxifen Anastrozole Trial
JCO	Journal of Clinical Oncology
Ki-67	Kiel-antigen 67 (proliferation marker)
KPS	Karnofsky performance score
LABC	Locally advanced breast cancer
LADO, LDF	Latissimus dorsi muscle flap
LCIS	Lobular carcinoma in situ
LDH	Lactat dehydrogenase
LHRH	Luteinizing hormone releasing hormone
LIN	Lobular intraepithelial neoplasia
LITT	Laser-induced thermotherapy
LN	Lobular neoplasia
Lnn.	Axillary lymph nodes
LoE / GR	Level of evidence / grade of recommendation (Oxford Centre for Evidence-based medicine)
Locoreg	Loco-regional
LRR	Loco-regional recurrence
LVEF	Left ventricular ejection fractions

Abbreviations – VI

MBC	Metastatic breast cancer
MDS	Myelodysplastic syndrome
Med	Median
Menop.	Menopause
MG / MS	Mammography / breast sonography
MIB	Minimal invasive breast biopsy
Mitox	Mitoxantrone
Mo / mo	Months
mod.	Modified
MPA/MA	Medroxyprogesterone acetate / megestrole acetate
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy
MTX	Methotrexate
MUGA	Multiple-gated acquisition scan
Mx	Mastectomy, mammography
n.s., ns	Not significant
N+	Node-positive
Nab-Paclitaxel	Nanoparticle-albumin-bound-paclitaxel
NAC	Nipple-areola-complex
NBS	National Breast Screening Study (Canada)
NCI-CTC2	National Cancer Institute – Common Toxicitiy Criteria
NEAT / SCTBG	National Epirubicin Adjuvant Trial / Scottish Cancer Trials Breast Group
Neg.	Negative
NMR	MRI
NSABP	National Surgery Adjuvant Breast and Bowel Project
NSABP B14	NSABP Breast trial 14
NSABP B17	NSABP Breast trial 17
NSABP B20	NSABP Breast trial 20
NSABP B-33	NSABP Breast trial 33
NSABP P1-trial	NSABP Prevention trial 1
NX	Vinorelbine / capecitabine
NYHA	New York Heart Association

Abbreviations – VII

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

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Abbreviations – VIII

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 Symosium
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

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

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- **The members of the editing committee of these guidelines are specialists in diagnosis, treatment, and research in breast cancer. Most of the members therefore have cooperations with industry. Thus, potential conflict of interest cannot be excluded.**
- **In order to minimize potential bias within the statements we followed the pre-defined rules:**
  - **These guidelines are strictly based on available evidence from the scientific literature.**
  - **The chapters of each edition were prepared by annually alternating teams of authors.**
  - **Each statement and the correspondent AGO-recommendations were thoroughly discussed within the entire group and accepted by majority decisions.**
  - **Each member of the editing committee is required to submit a written declaration of his/her conflicts of interests to an elected internal COI committee on an annual basis.**
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All members of the AGO Breast Committee have submitted their COI report for the past year. Members of the AGO Breast Committee indicated that they have received support (e.g. research funding, lecture or consulting honoraria etc.) from the following commercial entities:

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  AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2017 Liedtke C., Thill M., Jackisch C., Thomssen C., Müller V., Janni W., on behalf of the AGO Breast Committee Breast Care 2017;12: 172–183 (DOI:10.1159/000477575)

  AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2017 Thill M., Liedtke C., Solomayer E.-F., Müller V., Janni W., Schmidt M., on behalf of the AGO Breast Committee Breast Care 2017;12: 184–191 (DOI:10.1159/000477576)

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Options for Primary Prevention: Modifiable Lifestyle Factors

START

Prevention

- **Version 2011:**
  Gerber / Thomssen
- **Versions 2012–16:**
  Dall / Diel / Gerber / Maass / Mundhenke
- **Version 2017:**
  Mundhenke / von Minckwitz

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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**

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Further Information

References

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

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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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van Germert et al., Int J Cancer 2015; 152: 155-162

Secondary Prevention, Lifestyle and TNBC Subgroup

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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

Secondary Prevention, Lifestyle and ER-positive Subgroup

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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)

Nechuta et al., Int J Cancer, DOI 10.1002 (Epub ahead of print)

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Prevention by Changing Pregnancy Related Factors

	Oxford / AGO LoE / GR
➢ Any full term pregnancy	2b B
➢ Number of pregnancies	2b B
➢ First full term pregnancy before age of 30 years	2b B
➢ Breast feeding (protective if total breast feeding time exceeds 1.5–2 years)	3a B

Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

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	Oxford / LoE	AGO 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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Further Information

References

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Prevention by Changing Lifestyle Factors: Diet

	Oxford / LoE	AGO / GR	
➢ **Preference of a balanced 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	+
➢ Vegetarian diet (no risk reduction)	1b	B	+/-
➢ Vegan diet (no significant risk reduction)	1b	B	+/-

* As recommended by German Society of Nutrition (DGE)
* *Recommended as a part of healthy nutrition

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References

Prevention by Modifying Lifestyle Risk Factors: Alcohol

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	Oxford LoE	AGO GR
➢ **Reduction of alcohol intake reduces risk of breast cancer**	2b	B
Particularly for		
➢ **ER+/PgR+ tumors**	2b	B
➢ **Invasive lobular tumors**	2b	B

Prevention by Modifying Lifestyle Risk Factors: Smoking

Guidelines Breast
Version 2017.1

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

Prevention by Modifying Lifestyle Risk Factors: Physical Activity

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
➢ **Physical exercise**	2a(-)	B	++
(Metabolic equivalents to 3–5 hrs moderate pace walking per week)			

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

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	Oxford / AGO		
	LoE	GR	
➢ **Avoiding hormonal therapy in postmenopausal women**			
➢ **Avoiding estrogen / progestin combinations**	1b	A	+
➢ **Avoiding estrogens only**	1b	A	+/-

(no increasing risk for breast cancer by using estrogens alone, but increasing risk for endometrial cancer)

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Further Information

References

Prevention
Hormones in Postmenopausal Patients

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	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 secundary prevention side effects as comp. to WHI + cholcystectomy↗
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	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 +

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Further Information

References

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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

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	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

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Further Information

References

FORSCHEN
LEHREN
HEILEN

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

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

Guidelines Breast
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	Oxford LoE
➢ **Overall, OC does not significantly increase risk of cancer**	**1a**
➢ **Risk of breast cancer may be slightly increased, risk of ovarian, endometrial cancer is decreased**	**1a(–)**

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

Further information and references:

Screened data bases:
Pubmed 2005 - 2016, ASCO 2012 – 2016, SABCS 2012 – 2016, 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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2. Ritte et al.: Reproductive factors and risk of hormone receptor positive and negative breast cancer: a cohort study. BMC Cancer 2013 Dec 9;13:584.
3. Collaborative Group on Hormonal Factors in Breast Cancer: Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012 Nov;13(11):1141-51.

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

No further information

References:

1. Modified from American Cancer Society 2010 (http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors, last revised 31.12.2013)
2. Gaudet MM et al: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013 Apr 17;105(8):515-25.
3. Willhite CC et al: Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminium, aluminium oxides, aluminium hydroxide and its soluble salts. Crit Rev Toxicol 44/4: 1-80 (2014)
4. Van Germert et al., Int J Cancer 152: 155-162 (2015)
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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

References:

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187-95.
2. Lord SJ: Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: a case-control study. Cancer Epidemiol Biomarkers Prev. 2008 Jul;17(7):1723-30.
3. Ma H: Pregnancy-related factors and the risk of breast carcinoma in situ and invasive breast cancer among postmenopausal women in the California Teachers Study cohort. Breast Cancer Res. 2010;12(3):R35
4. Martin RM: Breast-feeding and cancer: the Boyd Orr cohort and a systematic review with meta-analysis. J Natl Cancer Inst. 2005;97:1446-57.
5. Li CI: Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu overexpressing breast cancer among women 20-44 years of age. Breast Cancer Res Treat. 2013;137:579-87.

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

No further information

References:

1. Simpson ER: Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013 Nov 26;51(3):T51-9.
2. Cheraghi Z: Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7(12):e51446. doi:
3. Chan DS: Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol. 2014 Oct;25(10):1901-14.
4. Brinton LA: Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst. 2014 Mar;106(3):djt465.
5. Pierobon, Breast Cancer Res Tr, 2013
6. Jiralerspong S, Goodwin PJ, Obesity and Breast Cancer Prognosis: Evidence, Challenges, and Opportunities JCO 2016, 34:4203-4216
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Prevention by Changing Life Style Factors: Diet (10/17)

No further information

References:

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2. Brennan SF: Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010 May;91(5):1294-302.
3. Cummings SR: Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst. 2009 Mar 18;101(6):384-98.
4. Zamora-Ros R: Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res Treat. 2013 May;139(1):163-76.
5. Rossi RE: The Role of Dietary Factors in Prevention and Progression of Breast Cancer. Anticancer Res. 2014 Dec;34(12):6861-6875.
6. Chlebowski RT: Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013 Aug;22 Suppl 2:S30-7.
7. Zheng JS, Hu XJ, Zhao YM, Yang J, Li D., Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ. 2013 Jun 27;346:f3706.
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9. Penniecook-Sawyers JA, et. Br J Nutr 2016

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

No further information

References:

1. Gerber B: Nutrition and lifestyle factors on the risk of developing breast cancer. Breast Cancer Res Treat. 2003 May;79(2):265-76.
2. Bagnardi V: Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2014 Nov 25. doi: 10.1038/bjc.2014.579. [Epub ahead of print]
3. Li CI: Alcohol Consumption and Risk of Postmenopausal Breast Cancer by Subtype: The Women's Health Initiative Observational Study. J Natl Cancer Inst 2010;102:1422–1431
4. Suzuki R: Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis of epidemiological studies. Int J Cancer. 2008 Apr 15;122(8):1832-41.
5. McDonald JA: Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. Curr Breast Cancer Rep. 2013 Sep;5(3).

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

No further information

References:

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

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

No further information

References:

1. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. Recent Results Cancer Res. 2011;188:125-39.
2. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2013 Feb;137(3):869-82.
3. Chlebowski RT: Nutrition and physical activity influence on breast cancer incidence and outcome. Breast. 2013 Aug;22 Suppl 2:S30-7.
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Prevention by Modifying Life Style Risk Factors: Hormone Therapy in Postmenopausal Women (14/17)

No further information

References:

1. Chlebowski RT: Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA (2010) 304: 1684–1692
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10. Chlebowski et al., J Natl Compr Canc Netw 2015, 13:917-24
11. Salagame et al., Int J Cancer 2015.

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
2. Gierisch JM:Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013 Nov;22(11):1931-43.
3. Moorman PG, Havrilesky LJ, Gierisch JM. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol. 2013 Nov 20;31(33):4188-98.

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Breast Cancer Risk and Prevention

START

Breast Cancer Risk and Prevention

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- **Versions 2003–2016:**
  Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Rody / Schmidt / Stickeler / Thomssen

- **Version 2017:**
  Schmutzler / Fasching

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Principles of 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

Inclusion criteria based on a mutation detection rate < 10% (in higher age groups):

- own disease of triple negative breast cancer ≤ 60 yrs. of age
- own disease with ovarian cancer

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

All mutation carriers should be registered in scientific databases, to validate the inclusion and exclusion criteria

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References

Checklist according to Public Health Insurance Policies (German GKV)*

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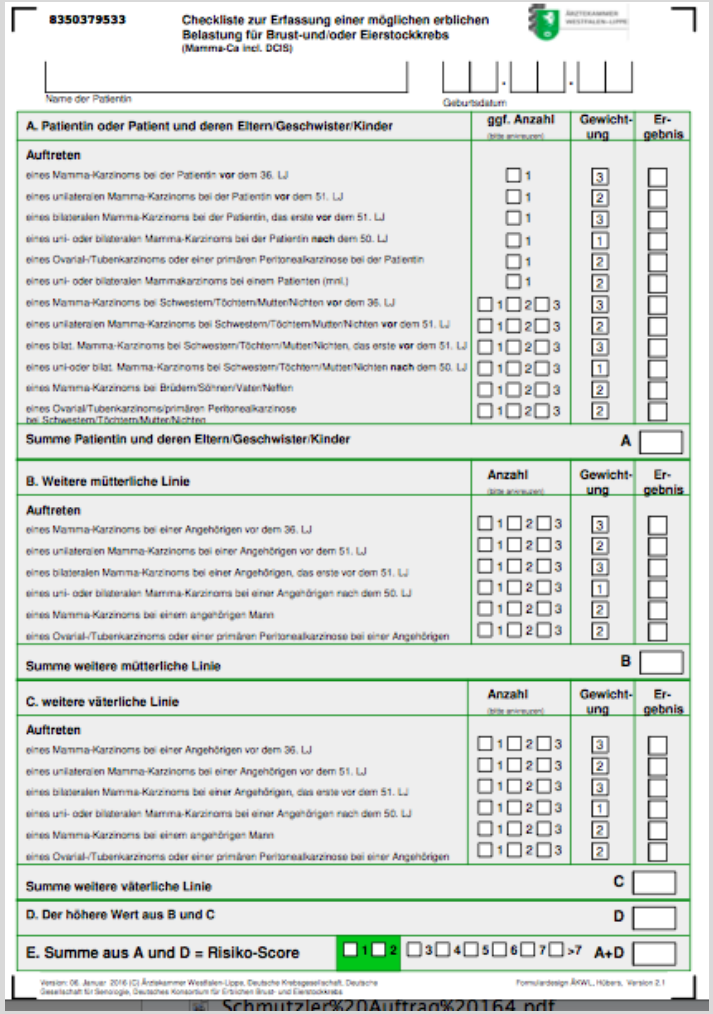


8350379533

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)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei der Patientin **vor** dem 36. LJ	☐1	3	☐
eines unilateralen Mamma-Karzinoms bei der Patientin **vor** dem 51. LJ	☐1	2	☐
eines bilateralen Mamma-Karzinoms bei der Patientin, das erste **vor** dem 51. LJ	☐1	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin **nach** dem 50. LJ	☐1	1	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin	☐1	2	☐
eines uni- oder bilateralen Mammakarzinoms bei einem Patienten (mnl.)	☐1	2	☐
eines Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **vor** dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **vor** dem 51. LJ	☐1☐2☐3	2	☐
eines bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten, das erste **vor** dem 51. LJ	☐1☐2☐3	3	☐
eines uni-oder bilat. Mamma-Karzinoms bei Schwestern/Töchtern/Mutter/Nichten **nach** dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei Brüdern/Söhnen/Vater/Neffen	☐1☐2☐3	2	☐
eines Ovarial/Tubenkarzinoms/primären Peritonealkarzinose bei Schwestern/Töchtern/Mutter/Nichten	☐1☐2☐3	2	☐
Summe Patientin und deren Eltern/Geschwister/Kinder			A ☐

B. Weitere mütterliche Linie	Anzahl (bitte ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	☐1☐2☐3	2	☐
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	☐1☐2☐3	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei einem angehörigen Mann	☐1☐2☐3	2	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	☐1☐2☐3	2	☐
Summe weitere mütterliche Linie			B ☐

C. weitere väterliche Linie	Anzahl (bitte ankreuzen)	Gewichtung	Ergebnis
Auftreten			
eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ	☐1☐2☐3	3	☐
eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ	☐1☐2☐3	2	☐
eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erste vor dem 51. LJ	☐1☐2☐3	3	☐
eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ	☐1☐2☐3	1	☐
eines Mamma-Karzinoms bei einem angehörigen Mann	☐1☐2☐3	2	☐
eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen	☐1☐2☐3	2	☐
Summe weitere väterliche Linie			C ☐
D. Der höhere Wert aus B und C			D ☐
E. Summe aus A und D = Risiko-Score	☐1☐2 ☐3☐4☐5☐6☐7☐>7		A+D ☐

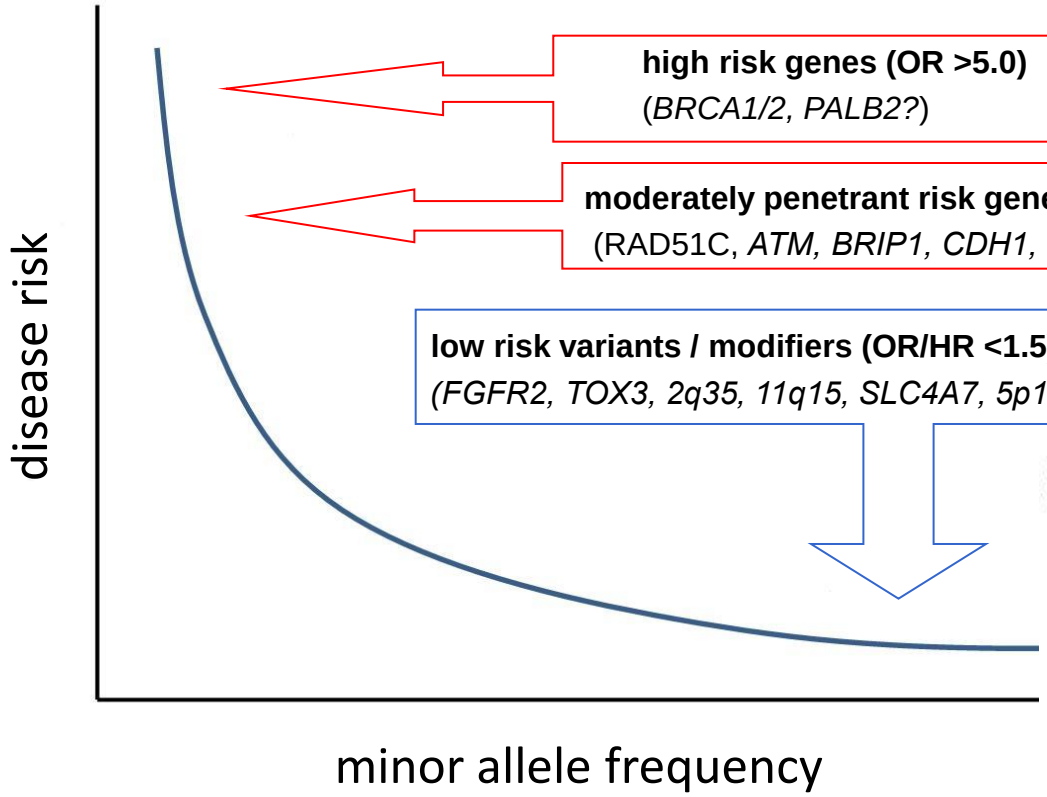
Version: 06. Januar 2016 (C) Ärztekammer Westfalen-Lippe, Deutsche Krebsgesellschaft, Deutsche Gesellschaft für Senologie, Deutsches Konsortium für Erblichen Brust- und Eierstockkrebs — Formulardesign ÄKWL, Höbers, Version 2.1

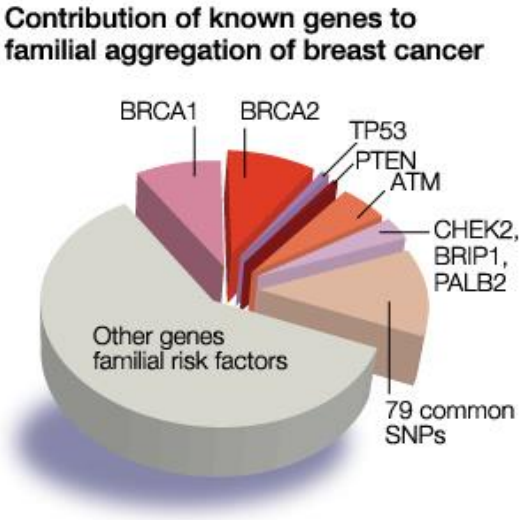
Schmutzler%20Auftrag%20164.pdf

*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

State of the Art

Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity





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Breast Cancer Risk Genes with a High Lifetime Risk

Only genes with a mutation frequency over 0.5% were considered for assessment.

	Oxford / AGO LOE	GR	
➢ **BRCA1, BRCA2**	2a	A	++
➢ **PALB2**	3a	B	+/-
➢ **ATM****	3a	C	-
➢ **CHEK2****	3a	C	-

*** BRCA1/2 are genes with a high lifetime risk. Furthermore genes with a medium and a low lifetime risk have been described.**
****These genes are classified as genes with a moderate lifetime risk based on the currently available data.**

Participation in prospective registries or studies is highly recommended.

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Further Information

References

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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 counseling: GCP

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Further Information

References

Clinically not validated Breast Cancer Gene Panels for Risk Prediction

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in der DGGG e.V.
sowie
in der DKG e.V.

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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 Ovarialkarziom (30 genes)

http://www.cegat.de/Tumorerkrankungen_171.html

- *ATM*
- *BARD1*
- *BRCA1*
- *BRCA2*
- *BRIP1*
- *CDH1*
- *CHEK2*
- *EPCAM*
- *FANCA*
- *FANCC*
- *FANCD2*
- *FANCE*
- *FANCF*
- *FANCG*
- *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*
- *FANCG*
- *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*

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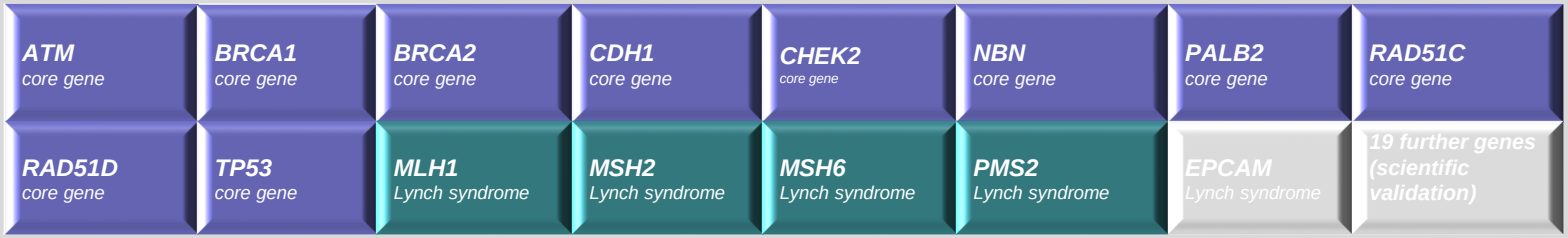
TruRisk® BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC



Gene selection:

10 BC/OC 'core genes' (sufficient data for genetic counseling)

5 HNPCC genes

19 BC/OC genes as part of scientific validation

Strategy:

- **Validation in large cohort, constant expansion and improvement**

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Further Information

References

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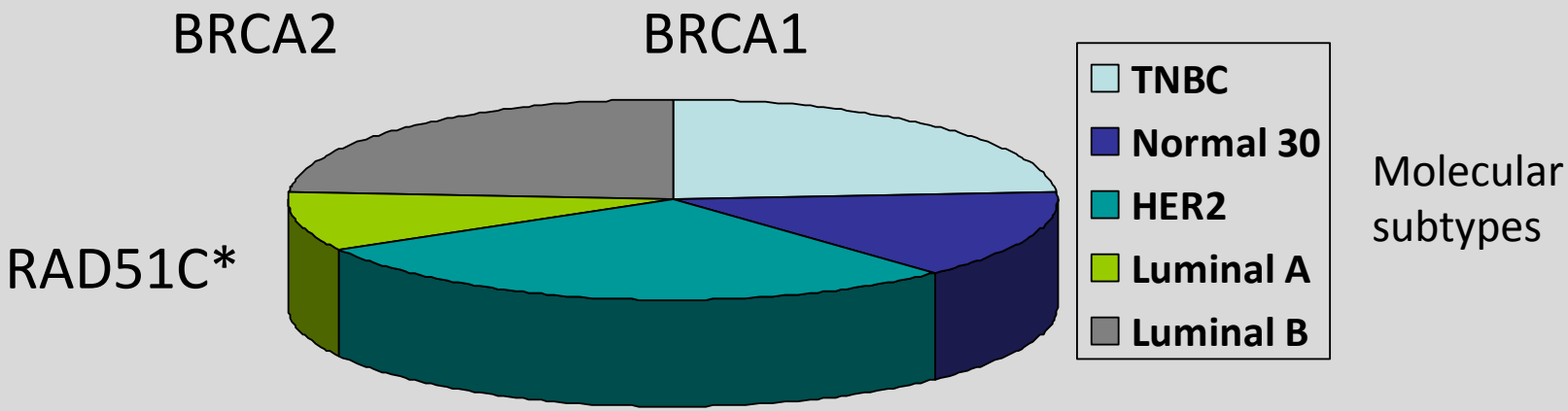
Clinical Implication: Genotype/Phenotype



*Meindl et al. Nat. Genet 2010

Gevensleben et al. 2013

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

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Further Information

References

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 adressed:
- 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

- „A **Variant of Unknown Significance (VUS)** is a genetic variant with unknown clinical relevance.“ (Plon et al. Hum Mutat 2008)
- Most VUS are private (>60%) or extremely rare (≤3, >80%)
- Additional analyses required, e.g. in vitro splicing assay, functional assay, segregation analysis, co-occurence 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

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

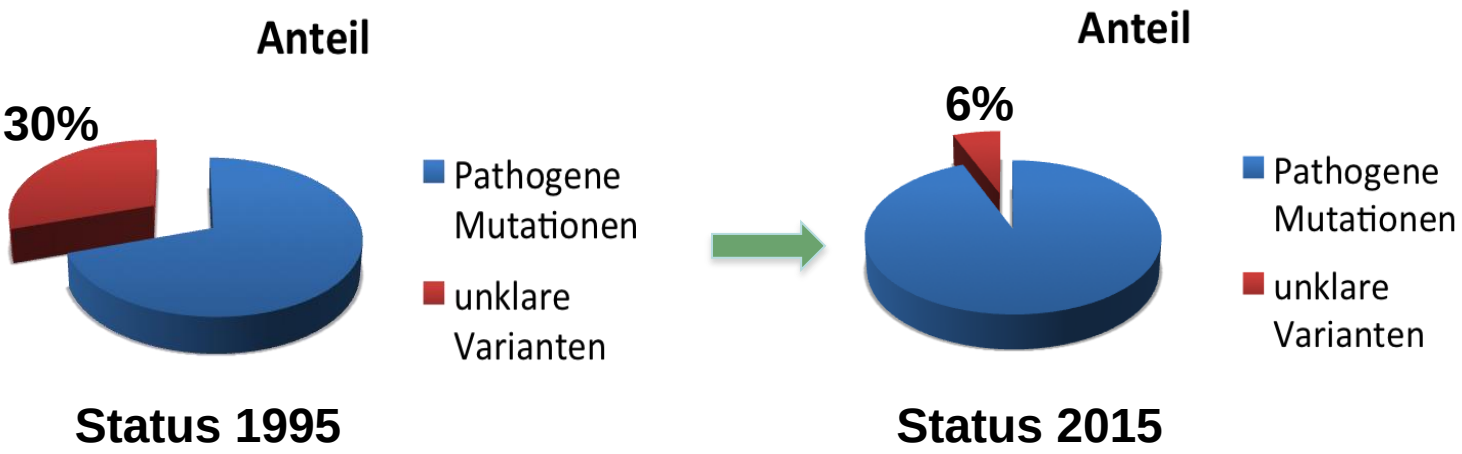
Only class 4 and 5 variants are considered clinically relevant

Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.

- Co-occurence 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*

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- The risk collective is clearly defined by risk criteria
- The positive predictive value of risk critiera 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

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Further Information

References

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.

	Oxford / AGO LoE	GR	
➢ Clinical genetic testing for *RAD51C; CHEK2* and/or other moderate risk genes, e.g. gene panels	3b	B	+/-
➢ Clinical genetic testing for low risk variants	3b	D	--
➢ Referral to centres of the GC-HBOC or cooperating centres	5	D	+

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Further Information

References

Non Directive Counseling for the Uptake of Preventive Measures

Oxford / AGO
LoE / GR

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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Further Information

References

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Definition of Women at Moderate to High Risk

	Oxford / AGO LoE	GR
➢ Deleterious mutation in the BRCA1, BRCA2	1a	++
➢ High risk (mutation probability of ≥ 10% OR heterozygous risk of ≥ 20% OR remaining life time risk of ≥ 30% acc. to a validated standard risk prediction models*	2b	+
➢ Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)	2a	++

*Caveat: Current breast cancer risk prediction programmes might not be validated yet or ready for clinical use.

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Further Information

References

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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 reduction of metastasis free survival**		**3a**	**B**	**+**

***Early detection / screening should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures**

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Further Information

References

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

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Version 2017.1

Further Information

References

		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**	**+/-***

***Follow up care / surveillance should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures**

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

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 <=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 <= 65y.

	Oxford / AGO LoE / GR		
Currently no specific surveillance is recommended			
➢ **For breast cancer prevention: self examination and watchful waiting**	**5**	**D**	**+**
➢ **For prostate cancer prevention: study participation if available**	**3b**	**C**	**+**

***Follow up care / surveillance should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures**

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References

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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**

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Further Information

References

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Surgical Prevention

	Oxford / AGO LoE / GR	
➢ **Unilateral or bilateral mastectomy is not indicated in the absense of clearly defined genetic risk factors**	**2a**	**B +***

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References

Guidelines Breast
Version 2017.1

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**	2c B ++*
reduces OvCa incidence and mortality	
reduces BrCa incidence and mortality	
reduces overall mortality	
➢ **Contralateral mastectomy (RR-BM, PBM)**	2c B +*
reduces BrCa incidence and mortality	

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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Further Information

References

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

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	Oxford / AGO LoE	GR	
➢ **Bilateral salpingo-oophorectomy (RR-BSO)** reduces OvCa incidence and mortality reduces BrCa mortality reduces overall mortality (contradictory results for reduction of cl BrCa incidence)	2b	B	+*
➢ **Contralateral mastectomy + (RR-BM)** reduces cl BrCa incidence and mortality	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**

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Further Information

References

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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 mestectomy 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**	**+**
➢ **gBRCA1/2 mutation status is predictive for chemotherapy response in TNBC**	**2b**	**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**

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Further Information

References

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Medical Prevention for Women at Increased Risk

	Oxford / AGO LoE / GR
➢ **Tamoxifen for women > 35 years** **Reduction of invasive BrCA, DCIS, and LN**	1a A +*
➢ **Raloxifen for postmenopausal women** **Reduction of invasive BrCa only**	1b A +*
➢ **AI for postmenopausal women**	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)**

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References

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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**

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Further Information

References

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

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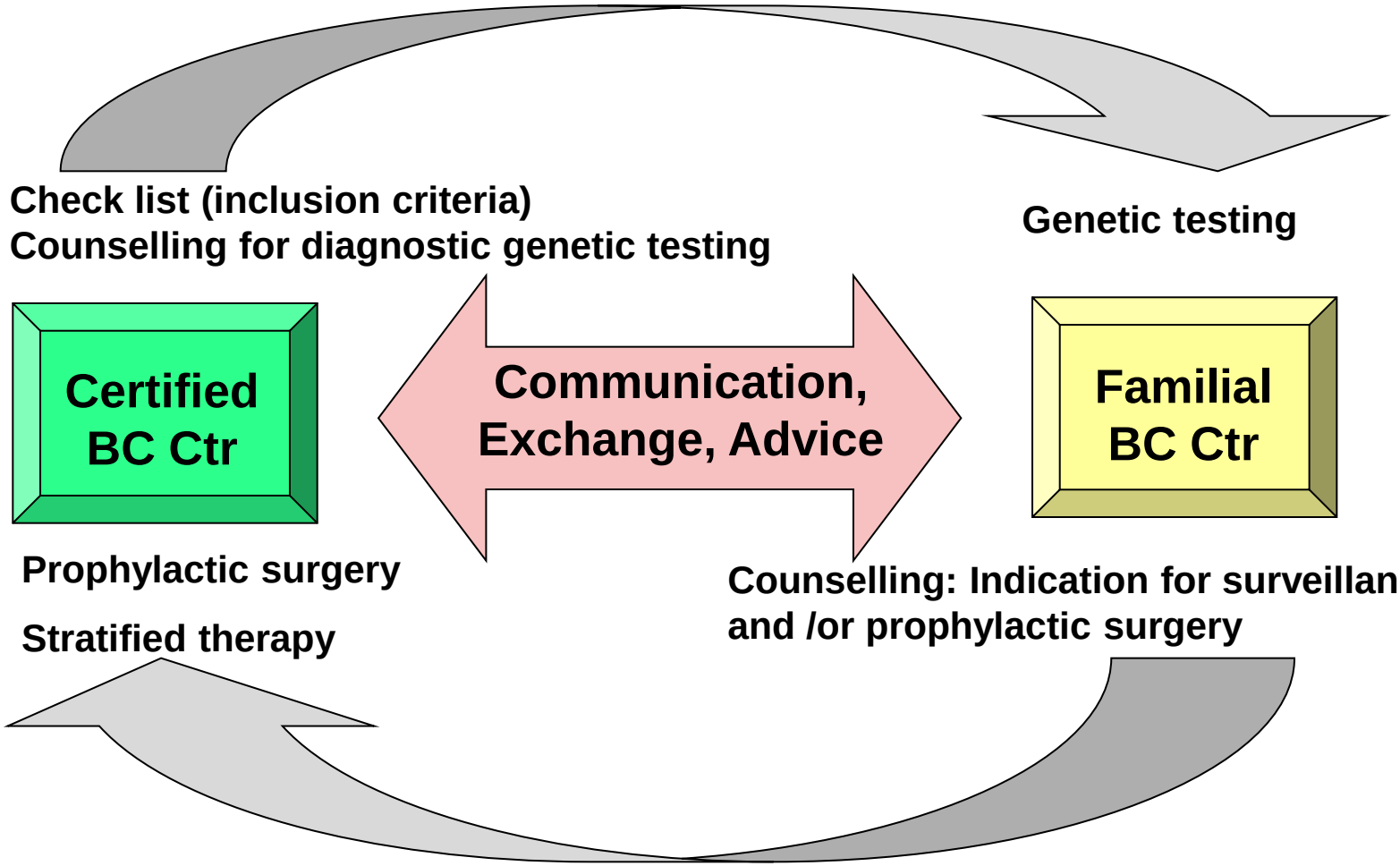

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015

Further Information
References

Breast Cancer Risk and Prevention (2/31)

No further information

No references

Principles of Prevention (3/31)

No further information

No references

Who should be Tested for BRCA1/2 Mutations? (4/31)

No further information

References:

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5. Harter P, Hauke J, Heitz F, Reuss A, Kommoss S, Marme F, et al. Incidence of germline mutations in risk genes including BRCA1/2 in consecutive ovarian cancer (OC) patients (AGO TR-1). J Clin Oncol 2016;34:(suppl; abstr 5538).
6. Meindl A, German Consortium for Hereditary B, Ovarian C. Comprehensive analysis of 989 patients with breast or ovarian cancer provides BRCA1 and BRCA2 mutation profiles and frequencies for the German population. Int J Cancer. 2002;97(4):472-80.
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Checklist according to Public Health Insurance Policies (German GKV)* (5/31)

No further information

No references

State of the Art – Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (6/31)

No further information

References:

1. Couch F, Shimelis H, Hu C, Lilyquist J, Na J, Polley EC, et al. Breast Cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 60,000 breast cancer patients. San Antonio Breast Cancer Symposium. 2016:Abstract S2-01.
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Breast Cancer Risk Genes with a High Lifetime Risk (7/31)

No further information

References:

1. Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkas K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-506.
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3. Couch F, Shimelis H, Hu C, Lilyquist J, Na J, Polley EC, et al. Breast Cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 60,000 breast cancer patients. San Antonio Breast Cancer Symposium. 2016:Abstract S2-01.
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Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (8/31)

No further information

References:

1. di Masi A, Antoccia A. NBS1 Heterozygosity and Cancer Risk. Curr Genomics. 2008;9(4):275-81.
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Clinically not Validated Breast Cancer Gene Panels for Risk Prediction (9/31)

No further information

References:

1. Kurian AW, Idos G, Culver J, Ricker CN, Koff R, Sturgeon D, et al. Safety of multiplex gene testing for inherited cancer risk: Interim analysis of a clinical trial. J Clin Oncol. 2016;34:(suppl; abstr 1503).

TruRisk® BC/OC Gene Panel (34 Genes) by the German Consortium GC-HBOC (10/31)

No further information

No references

Clinical Implication: Genotype/Phenotype (11/31)

No further information

References:

1. Gevensleben H, Garcia-Murillas I, Graeser MK, Schiavon G, Osin P, Parton M, et al. Noninvasive detection of HER2 amplification with plasma DNA digital PCR. Clin Cancer Res. 2013;19(12):3276-84.
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Genetically defined Subtypes are distinct Tumor Entities (12/31)

No further information:

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Variant Classification proposed by IARC (14/31)

No further information

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Surgical Prevention for Healthy Female BRCA1/2 Mutation Carriers (25/31)

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Prophylactic bilateral salpingo-oophorectomy (PBSO) reduces the risk for ovarian cancer in BRCA1/2 mutation carriers to >95% and the risk for breast cancer to 50% (Kauff et al NEJM 2002, Rebbeck et al. NEJM 2002). Short term HRT does not negate the protective effect of PBSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, PBSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend PBSO in mutation carriers after completion of childbearing around the age of 40.
Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.
For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).
The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be preceeded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)

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Cooperation of Certified Breast Cancer Centres with Familial BC Ctr of the GC-HBOC* (31/31)

No further information

No references

Guidelines Breast
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Early Detection and Diagnosis

START

Early Detection and Diagnosis

- **<u>Versions 2005–2016:</u>**
  Albert / Blohmer / Fersis / Junkermann / Maass / Scharl / Schreer

- **<u>Version 2017</u>:**
  Albert / Müller-Schimpfle

Guidelines Breast
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Early Detection Mammography

Age	Interval	Oxford LOE /	Oxford GR	AGO
< 40	na	-	-	- -
40–49	12–24	1b	B	+
50–69*	24	1a	A	++
70–74	24	1a	A	++
>75**	24	4	C	+

*National Mammography-Screening-Program
**health status + life expectacy more than 10 years

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Further Information

References

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Breast Cancer Mortality Reduction

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)

Breast Cancer Mortality Reduction

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 7cohort studies and metaanalysis of case-control studies

Oeffinger KC et al JAMA 2015;314

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Breast Cancer Screening
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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)*

[a]A 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]

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Further Information

References

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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

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Further Information

References

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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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Further Information

References

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Hellquist BN et al. Cancer 2011; 117(4) : 714-722

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Early Detection Sonography

	Oxford / LOE	AGO / GR	
➢ **Screening-Breast Sonography**	5	D	- -
➢ **Automated 3D-Sonography**	3b	C	- -
As an adjunct:			
➢ **Dense mammogram (density 3–4/composition C-D)**	2b	B	++
➢ **Elevated risk**	1b	C	++
➢ **Mammographic lesion**	2b	B	++
➢ **Second-look US (MRI-only detected lesions)**	2b	C	++

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Early Detection
Clinical Examination

	Oxford LOE	AGO 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		++

* May increase breast awareness

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Assessment of Breast Symptoms or Lesions

	Oxford / LOE	GR	AGO
➢ **Clinical examination**	3b	B	++
➢ **Mammography**	1b	A	++
➢ Additional Tomosynthesis (vs spot compression)	3b	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**

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Pretherapeutic Assessment and Staging

	Oxford / LOE / GR		AGO
➢ Clinical examination	5	D	++
➢ Mammography	2b	B	++
➢ Mammography + Tomosyntheses + Sonography	3b	B	+
added MRI	3b	B	-
➢ Sonography	2b	B	++
Axilla + FNP/CNB	2b	B	++
➢ MRI *	1b	B	+/-
➢ Minimally invasive biopsy**	1b	A	++

*** MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions. Individual decision for patients at high-risk, with dense breast (density 3-4/composition C-D), lobular invasive tumors, suspicion of multilocular disease. No reduction in reexcision rate.**

**** Histopathology of lesions if relevant for treatment**

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Further Information

References

MRI: Preoperative Staging

- **9 eligible studies (2 randomized trials; 7 comparative cohorts)**
- **3112 patients with BC**
- **MRI versus no-MRI:**
  - **Initial mastectomy 16.4% versus 8.1% [OR, 2.22 (P < 0.001); adjusted OR, 3.06 (P < 0.001)]**
  - **Re-excision after initial breast conservation 11.6% versus 11.4% [OR, 1.02 (P = 0.87); adjusted OR, 0.95 (P = 0.71)**
  - **Overall mastectomy 25.5% versus 18.2% [OR, 1.54 (P < 0.001); adjusted OR, 1.51 (P < 0.001)]**

N Houssami et al. Ann Surg 2013; 257

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

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

N Houssami et al. Ann Surg 2013; 257

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MRI Sceening (High-risk) Benefit

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

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 muatation carriers (M)

MRI Screening (High-risk) Problems

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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

Study	No. Cases	Overall accuracy (%)	Sens. (%)	Spec. (%)
Gilles et al 1995	172	70	95	51
Westerhof et al 1998	63	56	45	72
Bazzocchi et al 2006	112	80	79	68
Kuhl et al 2007	75	-	88	-
Baur et al 2013	58	-	79,3	

„Negative breast MRI findings should not be considered a sure marker of benignancy.“

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Further Information

References

Early Detection and Diagnosis (2/19)

Further information and references:

Screened data bases:
- Pubmed 2013 - 2016
- Medline 2013 – 2016
- Cochrane 2013 - 2016

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

(http://ecibc.jrc.ec.europa.eu/recommendations/list/3;Update 24.11.2016, Abruf 20122016)

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 impairement and better quality of life.
Professionals and women need to be infomed 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. (IARC 2016, European Commission 2016, ACS 2015, USPSTF 2016)

Meta-analysis and reviews from randomised trials:
Conclusion of the meta-analysis of the Independen 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 inivitation to mammography screening is estimated to be 20%."

Data from observational studies and registries:
The EUROCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: "the best "European" estimate of 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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Breast Cancer Screening – ACS Guideline Update 2015 (7/19)

No further information

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Breast Cancer Ccreening – 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 to 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 (Moss 2015)

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 hand held ultrasound (HHUS) 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.

There is no evidence that evaluated the comparative effectiveness or diagnostic accuracy of screening breast ultrasound as an adjunct to mammography among average-risk women aged 50 years and over (Gartlehner 2013, Health Quality Ontario 2016).
Immature but interesting data are the first results after 1 year of the RCT (J-Start, Japan) revealing a high sensitivity for adjunct ultrasound (n 36859) vs mammography alone (36139) for women 40-49 years with average risk and annual screening exam (91·1%, 95% CI 87·2-95·0 vs 77·0%, 70·3-83·7; p=0·0004), significantly lower specificity (87·7%, 87·3-88·0 vs 91·4%, 91·1-91·7; p<0·0001) a higher cancer detection rate (184 [0·50%] vs 117 [0·32%], p=0·0003) and cancer at lower stage 0 and I (144 [71·3%] vs 79 [52·0%], p=0·0194) (Ohuchi 2015).

Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3,4 breast composition C-D (ACR 2013, Müller-Schimpfle 2016)) permits detection of small, otherwise occult, breast cancers (Schaefer 2010). Potential adverse impacts for women in this intermediate risk group are associated with an increased recall and biopsy rate (Nothacker 2009, Corsetti 2008,. Supplemental ultrasound is associated with increasing costs (Corsetti 2011). 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 and limited. (Golatta 2013-2015, Choi 2014, Wojcinski 2013, Shin 2015, Brem 2015, Hellgren R 2016, Wilczek 2016, Ginger 2016) ,.

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 (Lauby-Secretan 2015, IACR 2016). This is in line with the recommendations of the U.S. Preventive Services Task Force (Melnikow 2016). Women need to be informed about their benefit and harms of ultrasound

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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 (Thomas D 2002, Kosters J 2003). 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 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 ~2 ¼ 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 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.

References:

Combined DM + DBT + US + MRI

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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 Familiar 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

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MRI and DCIS (19/19)

No further information

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Guidelines Breast
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Pathology

START

Pathology

- **Versions 2004–2016:**
  Blohmer / Costa / Fehm / Friedrichs / Huober / Kreipe / Lück / Sinn / Thomssen

- **Version 2017:**
  Sinn / Schneeweiss

General Principles for Histopathologic Examination of Breast Cancer Specimens

- **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

	Oxford LoE	/ GR	AGO
➢ Minimize time to fixation (cold ischemia time)	5	D	++
➢ Minimal fixation time of 6 hours for optimal antigen preservation	5	D	++
➢ Optimal fixation time 6 - 72 h for core biopsies	5	D	++
➢ Optimal fixation time for resection specimens: 12 - 72 h	5	D	++
➢ Use of neutral buffered formalin	5	D	++

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Use of Fine Needle Aspiration Cytology*

	Oxford / LoE	GR	AGO
➢ Nipple secretion	5	D	+
➢ Tumor	5	D	-
➢ Cyst	5	D	+/-
➢ Lymph node	5	D	+/-

* Ultrasound-guided core biopsy recommended

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Workup: Macroscopy and Specimen Radiography

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

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

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

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Workup: Breast-Conserving Specimens

	Oxford LoE	/ GR	AGO
➢ 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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	Oxford / AGO LoE / GR		
➢ Margins always to be sampled - Skin close to tumor, at least 2 directions - Deep margin - Other margins, if close (< 1 cm)	5	D	++
➢ Attention to soft tissue margins in skin sparing mastectomy	5	D	++
➢ Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region	5	D	++
➢ More extensive sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)	5	D	++

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Workup: Sentinel Node Biopsy

	Oxford / LoE	AGO / GR	
➢ 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	-

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Indications for Immediate Pathological Analysis Including Frozen Sections

	Oxford / LoE /GR		AGO
➢ **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
➢ **Histologic tumor typing according to WHO-Classification, (4th ed., 2012)**	3b	C	++

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

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Reporting: Grade of Malignancy

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

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Reporting: Tumor Size and Total Extent of Tumor

	Oxford LoE	Oxford GR	AGO
➢ Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results	5	D	++
➢ Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality	5	D	++
➢ Reporting of size of noninvasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2x invasive Ca)	5	D	++

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Version 2017.1

Reporting: pTNM

	Oxford LoE / GR	AGO
➢ Use of current UICC classifikation (7th ed.)	5 D	++

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.

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Reporting: Margins of Resection and R-Classification

	Oxford LoE	Oxford 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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References

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Reporting: Lymphovascular Invasion

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

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FORSCHEN
LEHREN
HEILEN

Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

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	Oxford LoE / GR		AGO
➢ **Identification of tumors with predominant lymphocytic infiltrate (> 50%) in tumor stroma (according to Salgado et al.*)**	**5**	**D**	**+/-**

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., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014.**

Annals of Oncology

Reporting: Evaluation after Neoadjuvant Chemotherapy

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	Oxford LoE	/ GR	AGO
➢ 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	++
➢ Repeat IHC for ER, PgR, and HER2	4	D	+/-

Special Studies: ER-Testing by IHC

	Oxford / LoE	GR	AGO
➢ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
➢ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%, low pos. if≥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

	Oxford / LoE	AGO / GR	
➢ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
➢ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%)	1a	A	++
➢ Staining intensity of pos. tumor nuclei (0 - 3)	4	D	+
➢ Allred Score (0 - 8), Remmele Score (0 - 12)	4	D	+

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Additional Special Studies: Molecular Analysis of ER/PgR Status

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	Oxford / AGO LoE / GR		
➢ Evaluation of hormone receptors using validated gene expression test kits	3b	A	+/-
➢ Evaluation of hormone receptor by RNA-sequencing	5	D	-
➢ Use of molecular receptor analysis for subtyping	3b	A	+

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References

Special Studies: HER2 Testing

	Oxford / LoE / GR		AGO
➢ 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)	1a	A	++
➢ 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	++

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HER2 Testing on Core Biopsies

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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

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Further Information

References

Additional Special Studies: Molecular Analysis of HER2 Status

Guidelines Breast
Version 2017.1

	Oxford / LoE	AGO / 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	+/-

Guidelines Breast
Version 2017.1

Special Studies: Evaluation of Ki-67 Score

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

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Further Information

References

Intrinsic Breast Cancer Types (Molecular and Immunohistochemical Definitions)

Guidelines Breast
Version 2017.1

- **Currently there is no generally accepted and proven translation of molecularly defined types (basal, luminal A/B-Typ, HER2) into immunohistochemical counterparts neither with regard to markers nor to thresholds**
- **In terms of practical consequences re-labelling of clinically established and immunohistochemically defined subgroups might be useful (ER/PR+ for luminal, HER2+ for HER2-type, triple negative for basal type)**
- **The basal type shows an 80% overlap with the triple negative subgroup of ductal invasive breast cancer (ER <1% & PgR <1% & HER2 0/1+2+ (non-amplified, ratio <2))**
- **None of the available markers (Ki-67, grading, recurrence score etc.) can reliably discriminate between luminal A and luminal B type**
- **Although derived from RNA expression studies, RNA measurements are not suited for the definition of intrinsic types for purposes of therapy**

Quality Assurance: Immunohistochemistry

- **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)**

Guidelines Breast
Version 2017.1

Quality Assurance: HER2-Status

- **Continuous documentation of HER2 tests**
- **Quality goal: Rate of HER2-positivity: 15%±5%**
- **Use of standardised and validated HER2 test kits**
- **Participation in ring trials**

Guidelines Breast
Version 2017.1

Quality Assurance: Reporting

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

Pathology (2/30)

Further information:

This chapter contains basic recommendations for routine procedures in pathology. It is not intended to replace detailed protocols for the evaluation of operative specimens or for special studies. It is highly recommended to adhere to national quality assurance protocols concerning all aspects of working up and reporting of pathology specimens removed from women with breast cancer. Further information can be found in the following reports:

Screened data bases: PubMed 1970 – 2014

Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.I.2014Cochrane: Decision aids for risk communication update 2009
- EUSOMA position paper: Diagnosis of breast disease
- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition

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

No further information

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Use of Fine Needle Aspiration Cytology (5/30)

No further information

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Workup: Core Needle Biopsies (US-guided or stereotactic) (7/30)

No further information

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Statement: Routine workup in step sections

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Statement: Turn-around time < 24h

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Workup of Breast-Conserving Specimens (8/30)

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Workup of Mastectomy Specimens (9/30)

No further information

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Workup: Sentinel Node Biopsy (10/30)

No further information

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Statement: Evaluation of sentinel node biopsy:

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Statement: Full workup using step sections of ≥ 500 µm on paraffin embedded tissue

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Statement: Frozen section

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Statement: Imprint cytology instead or in addition of frozen section

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

No further information

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Statement: Lesions ≥ 1 cm, without core biopsy

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Statement: Non-palpable lesions or lesions < 1 cm

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Reporting: Histologic Tumor Type (12/30)

No further information

References:

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Reporting: Grade of Malignancy (13/30)

No further information

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Reporting: Tumor Size and Total Extent of Tumor (14/30)

No further information

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No further information

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Reporting: Margins of Resection and R-Classification (16/30)

No further information

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Intrinsic Breast Cancer Types (27/30)

No further information

No references

Quality assurance: Immunhistochemistry (28/30)

No further information

References:

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Quality assurance: HER2-Status (29/30)

No further information

No references

Quality assurance: Reporting (30/30)

No further information

No references

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Version 2017.1

Prognostic and Predictive Factors

START

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Version 2017.1

Prognostic and Predictive Factors

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

- **Version 2017:**
  Harbeck / Rody

Definition

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**

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“Low absolute risk implies low absolute benefit”

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Lancet 379: 432-444, 2012

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 (LoE_{2009}) and category of tumor marker study (CTS)**
  - **Clinical relevance for treatment decisions**

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Further Information

References

[1]Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
[2]Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
[3]McShane, 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

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

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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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Further Information

References

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

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.**

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012

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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/m²)	1b	B	+

* NACT = Neoadjuvant Chemotherapy

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Further Information

References

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	+

§ Validated clinical data only available for this assay

Commercially Available Molecular Tests

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	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-/+, < 70 years	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)« CE-Mark (fresh tissue and FFPE)	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

Commercially Available Molecular Tests

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	70 gene signature (MammaPrint®) $	21 gene Recurrence score (Oncotype DX®) $	8 gene signature (Endopredict®) $	PAM 50 (Prosigna®) $
Prognosis after 5 yrs (late recurrences)	not separately shown	no	yes	yes
Predictive impact (chemotherapy benefit)	poorly validated	yes *	not shown	not shown
Prospective-retrospective evidence (% of recruited patients)	Multicenter validation	NSABP B-14 **(14%)** NSABP B-20 **(28%)** ECOG 9127 SWOG 8814 **(40%)** ATAC **(30%)**	ABCSG 6 **(19%)** ABCSG 8 **(36%)** GEICAM-9906 **(45%)** ATAC **(10%)**	MA.12 **(59%)** MA.5 **(66%)** ABCSG 8 **(44%)** ATAC **(16%)**
Prospective evidence (5-year DFS, OS)	MINDACT (N0, N1)	$TAILOR_X$ (N0, low-risk, RS<11) PlanB (N0, high-risk/N+)	-	-

$ Validated clinical data only available for this assay
*** Trial performed bevore HER2 testing, HER2 positive patients may have been included**

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Further Information

References

Prospective Randomised Trials

(Oncotype DX [TailorX, PlanB], MammaPrint [MINDACT])

Prognosis in the low-risk group is for both tests favourable
(94% 5-Jahres DFS with adjuvant endocrine therapy only)

	TailorX	PlanB	MINDACT
Follow-up period	Median 69 mo	5-yr-DFS	Median 60 mo
Proportion of low risk patients (study population suitable for chemotherapy)	16 %	15.3 %	23.2 % (high clinical and low genomic risk)
Test failure rate	n.r.	2.9 %	26 % (fresh frozen tissue)
Proportion of intermediate risk patients (applies only to OncotypeDX)	67.3 %	60.4 %	n.a.
10-yr-follow up	----	----	----

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	+/-
➢ CTC before NACT (regarding OS, DDFS, LRFI)	I[a]	B	+/-
➢ Therapy decisions based on CTC phenotypes	III	C	-
➢ Multigene assays			
➢ EndoPredoct®, Prosigna® (N0-1, HR+, Her2 -)	I	B	+*
➢ 70 gene signature (MammaPrint®) (N0-1)	I	A	+*
➢ Oncotype DX® (N0-1, HR+ HER2-, 5 Jahre)	I	A	+*
➢ IHC4 (central pathology published algorithm) #	I	B	+/-

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Further Information

References

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LEHREN
HEILEN

*** 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

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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Version 2017.1

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	+
➢ *PIK3CA* mutation	I	B	B	+/-
➢ gBRCA in TNBC	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)

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Further Information

References

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Version 2017.1

Predictive Factors – Endocrine Therapy

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/m²)	2b	B	+/-

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Further Information

References

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Version 2017.1

Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

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 Information

References

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

Prognostic Factors – Metastatic Breast Cancer

Factor	LoE_{2009}	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	-*

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Further Information

References

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* Study participation recommended

Prognostic and Predictive Factors (2/21)

Further information:

Data bases screened: Pubmed 2008 - 2016, ASCO 2003 – 2016, SABCS 2003 – 2016, Cochrane data base (n.d.)

Guidelines screened:

St. Gallen 2015: Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thürlimann B, Senn HJ; 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.

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General References:

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Definition (3/21)

No further information

References:

See general references

Low Absolute Risk Implies Low Absolute Benefit (4/21)

No further information

References:

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Quality Criteria (5/21)

No further information

References:

1. Febbo PG, Ladanyi M, Aldape KD, Marzo AM de, Hammond ME et al. (2011) NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 9 Suppl 5: S1-32; quiz S33.
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Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination (6/21 and 7/21)

No further information

References:

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2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452

Requirements of a Marker-Based test to Reach Level IB Evidence (8/21)

No further information

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1. McShane LM, Hayes DF. Publication of tumor marker research results: the necessity for complete and transparent reporting. J. Clin. Oncol. 2012; 30(34): 4223 – 4232
2. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J. Natl. Cancer Inst. 2009; 101(21): 1446 – 1452

Prognostic Factors I in Early Breast Cancer (9/21)

No further information

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Also see general references.

1. Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, Hammond EH, Kuderer NM, Liu MC, Mennel RG, Van Poznak C, Bast RC, Hayes DF; American Society of Clinical Oncology. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016 Apr 1;34(10):1134-50.
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Statement: Obesity

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Reproducibility (10/21)

No further information

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Prognostic Factors II in Early Breast Cancer (11/21 and 12/21)

No further information

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ER/PR

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Ki-67

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Prospective randomized trials (15/21)

No further information

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Neoadjuvant Systemic Chemotherapy – Response Prediction I (17/21)

No further information

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See general references

Neoadjuvant Systemic Chemotherapy – Response Prediction II (18/21)

No further information

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TIL

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Predictive Factors – Endocrine Therapy (19/21)

No further information

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Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy (20/21)

No further information

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HER2: see chapters anti-HER2 therapy in early and metastatic setting

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Prognostic factors – Metastatic breast cancer (21/21)

No further information

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Lesions of Uncertain Malignant Potential (B3)

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

START

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

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- **Versions 2005–2016:**
  Albert / Audretsch / Brunnert / Fersis / Friedrich / Friederichs / Gerber / Kreipe / Nitz / Rody / Schreer / Sinn / Thomssen

- **Version 2017:**
  Huober / Kreipe

Pathology Reporting for Minimal Invasive Biopsies

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Version 2017.1

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**

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References

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

B3-Lesions

- **Lesions with risk of associated DCIS or invasive Ca:**
  - **Atypical ductal hyperplasia (ADH)**
  - **Lobular neoplasia (ALH, LCIS)**
  - **Flat epithelial atypia (FEA)**

- **Inhomogenous lesions with sampling risk:**
  - **Phyllodes tumor, cellular fibroadenoma**
  - **Atypical papilloma, if incompletely removed**
  - **Radial scar, complex sclerosing lesion**

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

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Version 2017.1

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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	Oxford / AGO LoE	GR	
➢ **Interdisciplinary conference: Concordant findings in pathology and imaging?**			
→ yes: proceed according to histologic type	3a	C	++
→ no: open biopsy	3a	C	++
vacuum assisted biopsy (after core biopsy)	5	D	+

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Atypical Ductal Hyperplasia (ADH)

- 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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References

Strategy after Diagnosis of ADH in Core Biopsy

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	Oxford / AGO LoE	GR	
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

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Further Information

References

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

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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

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

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References

Lobular Intraepithelial Neoplasia (LIN)

- 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

Variants of Lobular Neoplasia

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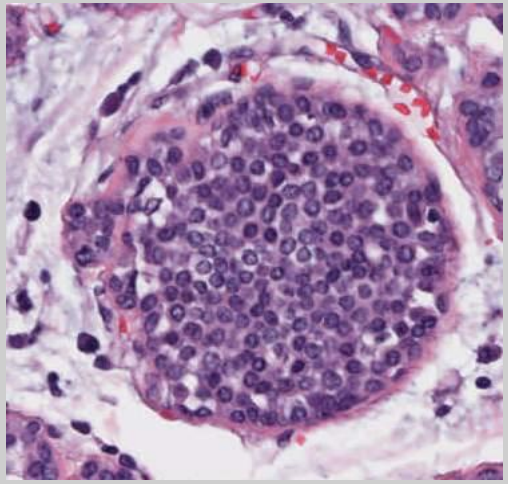
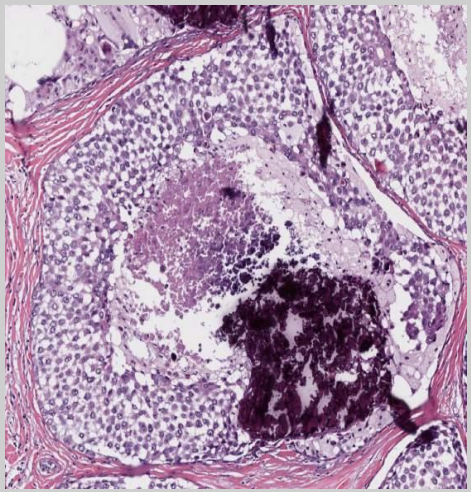
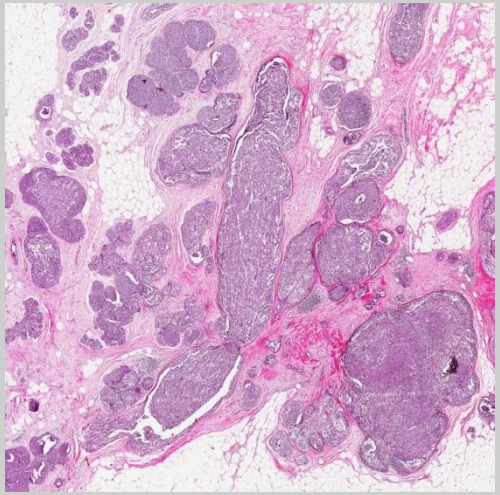


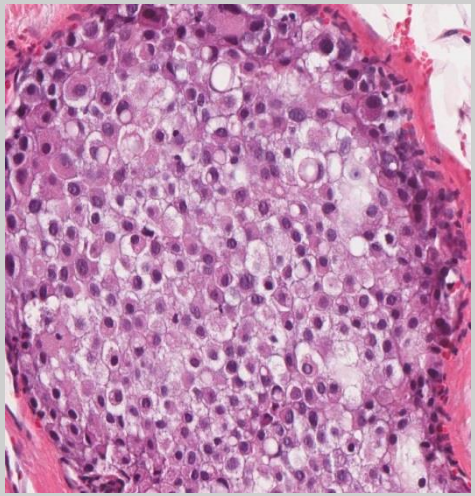
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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LIN with High Risk

- Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necroses, microcalcifications
- Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighbouring TDLU
- Type of LCIS with 21 cases of LCIS with microinvasion*:
  - classical LCIS: n=11
  - florid LCIS: n=4
  - pleomorphic LCIS: n=1

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

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Strategy after Diagnosis of LIN

	Oxford / AGO LoE	GR	
➢ **LIN in core- / vacuum-assisted biopsy:**			
→ Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings	**2b**	**C**	**++**
➢ **LIN at margins of resection specimen (BCT):**			
→ No further surgery	**2a**	**C**	**++**
Exceptions:			
a) Pleomorphic LIN, florid LIN, or LIN with necrosis b) Imaging abnormality is not removed			
→ Complete resection	**5**	**D**	**++**

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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.

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Strategy after Diagnosis of FEA

	Oxford / AGO LoE	GR	
➢ **FEA in core biopsy/vacuum-assisted biopsy:**			
→ Open excisional biopsy	3b	C	+
→ Open excisional biopsy may be omitted, with: a small lesion (≤ 2 TDLU* in vacuum biopsy) and complete removal of imaging abnormality	5	C	+
➢ **FEA at margins in resection specimen:**	3b	C	++

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

* Terminal ductal-lobular unit

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Papilloma

- Includes: Central 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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	Oxford / AGO LoE	GR	
➢ **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	++
<u>Papilloma at resection margin:</u>			
→ **no published data available**			

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Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radical 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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References

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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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	Oxford / AGO LoE / GR		
➢ **Radial scar / CSL in core biopsy/ vacuum-assisted biopsy:**			
→ Open excisional biopsy	3b	C	+
→ Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality	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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	Oxford / AGO LoE / GR
FEA, non-atypical papilloma	
➢ Screening mammography	5 C ++
LIN	
➢ Mammography (12 months)	3a C ++
ADH	
➢ Mammography (12 months)	3a C ++
➢ Women with LIN and ADH should be informed about their elevated risk of breast cancer	3a C ++

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References

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

	Oxford / AGO LoE	GR	
➢ Tamoxifen for women >35 years – Risk reduction of invasive BrCa and DCIS	1a	A	+
➢ Raloxifen for postmenopausal women - Risk reduction of invasive BrCa only	1b	A	+/-*
➢ Aromatase inhibitors (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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References

Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen)

NSABP-P1 Study, update 2005

	Placebo **Rate / 1000 WE**	**Tamoxifen Rate / 1000 WE**	**RR**	**95% CI**
All women	6.29	3.59	0.57	0.46-0.70
± LCIS	5.93	3.41	0.58	0.46-0.72
+ LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
+ ADH	10.42	2.55	0.25	0.10-0.52
5-year risk <2%	4.77	3.18	0.67	0.43-1.01
5 year risk > 5%	11.98	5.15	0.43	0.28-0.64
Relative 1.grade	6.47	3.48	0.54	0.34-0.83
> 3 relatives 1. grade	11.24	5.48	0.49	0.16-1.34
Fraktures	2.88	1.97	0.91	0.51-0.92
Endometriumcancer	0.68	2.24	3.28	1.87-6.03

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

- **LIN, ADH**
- **Family history of breast cancer**

Should not be offered to women:

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

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References

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

Guidelines Breast
Version 2017.1

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.

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Further Information

References

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 ≥1,66%) or postmeopausal

Should not be offered to women:

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

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Further Information

References

Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors)

Guidelines Breast
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Inclusion criteria:	Results for prior ALH, ADH, LCIS (HR AI vs Plac):
➢ IBIS.2:	
➢ Prior ADH, ALH, or LCIS Anastrozole:154 (8.0%); Placebo: 190 (9.7%)	➢ 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)

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Further Information

References

Cuzick J et al. Lancet 2014; 383: 1041–48
Goss PE et al. N Engl J Med. 2011 Jun 23;364(25):2381-91

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

Further information and references:

Pubmed 2010-2016 (plus earlier publications if relevant):
Lobular neoplasia (186 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 (256 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 (105 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 (288 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 (29 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 Guidelines:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.I.2014
- NCCN Breast Cancer Risk Reduction I 2013
- NCCN Breast Cancer Screening and Diagnosis 2.2013
- NZ: HTA risk assesment 2007
- CMJA: no update
- NICE: no update
- SIGN: no update
- Cochrane: Decision aids for risk communication update 2009
- DARE: no relevant references. 2010
- ASCO 2012: done
- National Institute of health (NIH): done
- San Antonio Breast Cancer Conference (SABCC 2013): done

Further references:

National and international guidelines

Albert US, Altland H, Duda V et al. 2008 update of the guideline early detection of breast cancer in Germany. J Cancer Res Clin Oncol 2009; 135:339-354
Albert US, (Hrsg). Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 1.Aktualisierung 2008. 1 ed. Muenchen: Zuckschwerdt Verlag, 2008.
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Lebeau A, Kreipe H, Dietel M, Schlake W, Kreienberg R. Mammakarzinom: aktuelle Empfehlungen fur Pathologen auf Basis der S3-Leitlinie. Pathologe. 2013;34(4):293-302
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Weir R, Day P, Ali W. Risk factors for breast cancer in women:a systematic review of the literature. Christchurch: New Zealand Health Technology Assessment (NZHTA), 2007.
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NCCN, National Comprehensive Cancer Network. Breast cancer risk reduction V.I.2013. 2013 ed. USA: NCCN, 2013.
NCCN, National Comprehensive Cancer Network. Breast cancer screening and diagnosis V.2.2013. 2013 ed. USA: NCCN, 2013.
O'Connor A, Bennett C, Stacey D et al. Decision aids for people facing health treatment or screening decisions (Review). The Cochrane Library 2009;(4):1-35.

Pathology Reporting for Minimal Invasive Biopsies (3/25)

Further information:

The histologic B-classification of breast core biopsies as based on recommendations of the National Coordinating Group for Breast Screening Pathology (NHSBSP), and E. C. Working Group on breast screening pathology encompasses the heterogeneous B3 category.

References:

1. World Health Organization: WHO Classification of Tumours of the Breast. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, editors. World Health Organization; 2012.
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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 partiularly obvious for LIN, which only rarely shows upgrade to higher lesions in resection when carful 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% disconcordance among first and second pathology compared to 0.5-1,3% disconcordance 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 patholgy 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 asoziated with postmenopausal hormone treatment. According to the data of the Breast Cancer Surveillance Consortium (USA) rates of ADH decreased from 5.5/10000 mammograms 1999 to 2.4/10000 mammograms in 2005

Statement: indicator-/ precursor-lesion:
Women have an enhanced breast cancer risk after ADH: one lesion RR 3.88 (95%CI 3.00-4.94), three lesions RR10.35 (95%CI 6.13-16.4). Less than 45 years at diagnosis of ADH RR 6.78 (95%CI 3.24-12.4).

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Strategy after Diagnosis of ADH in Core Biopsy(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 supicious 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)

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

No further information

References:

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Lobular Intraepithelial Neoplasia (LIN) (10/25)

Further information:

Lobular neoplasia (LN) or lobular intraepithelial neoplasia (LIN) are the preferred terms for early neoplasia with lobular phenotype and include atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). For a long time, LN was considered to be just as a risk indicator and not a precursor lesion for the subsequent development of carcinoma. More recently, because of pathological and molecular studies, it is now believed that lobular neoplasia indeed is a non-obligatory precursor of invasive carcinoma, and at the same time a risk lesion for ipsi- and contralateral disease. Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, florid LCIS and pleomorphic LCIS were shown to be 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 neeedle, or on vacuum-assisted biopy, 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 be completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.

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Statement: Indicator-/ precusor 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 be 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).

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3. Shin SJ, Lal A, De Vries S, Suzuki J, Roy R, Hwang ES, Schnitt SJ, Waldman FM, Chen YY. Florid lobular carcinoma in situ: molecular profiling and comparison to classic lobular carcinoma in situ and pleomorphic lobular carcinoma in situ. Hum Pathol. 2013;44(10):1998-2009.

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 be 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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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)

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LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a)

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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 tubulär 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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Statement: Marker Lesion (LoE 3b)

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Strategy after Diagnosis of FEA (15/25)

Further information:

If a FEA is detected in core biopsy further no further (open) biopsy is indicated if the underlaying 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)

No further information

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

No further information

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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 absolut terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

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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 +)

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IBIS.1

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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

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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 absolut terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

References:

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

No further information

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3. Vogel V: Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P2 trial. JAMA 2006; 295(23):2727-2741.
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Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors) (25/25)

No further information

References:

Exemestane for breast-cancer prevention in postmenopausal women.

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

1. Bozovic-Spasojevic I[1], Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F.

Guidelines Breast
Version 2017.1

Ductal Carcinoma in Situ (DCIS)

START

Ductal Carcinoma in Situ
DCIS

- **Version 2002:**
  Gerber

- **Versions 2003–2016:**
  Audretsch / Blohmer / Brunnert / Costa / Fersis / Friedrich / Hanf / Junkermann / Kühn / Lux / Maass / Möbus / Nitz / Oberhoff / Scharl / Solomayer / Souchon / Thill / Thomssen

- **Version 2017:**
  Budach / Fersis

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Version 2017.1

Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

	Oxford / AGO LoE	GR	
➢ **Mammography**	1b	A	++
➢ Magnification view of microcalcification	4	C	++
➢ Increase of detection rate 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	1b	B	+/-
➢ **Clinical examination**	5	D	++
➢ **FNA / ductal lavage**	5	D	-
➢ **Interdisciplinary board presentation**	5	D	++

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Further Information

References

MRT und DCIS

Studie	Anzahl Unter-suchungen	Zuverlässig-keit (%)	Sensiti-vität (%)	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."

Guidelines Breast
Version 2017.1

MRI and DCIS

Systematic review

Meta-analysis of the effect of preoperative breast MRI on the surgical management of ductal carcinoma *in situ*

A. Fancellu[1], R. M. Turner[2], J. M. Dixon[4], A. Pinna[1], P. Cottu[1] and N. Houssami[3]

[1]Department of Clinical and Experimental Medicine, Unit of General Surgery 2, Clinica Chirurgica, University of Sassari, Sassari, Italy, [2]School of Public Health and Community Medicine, The University of New South Wales, and [3]Screening and Test Evaluation Programme, School of Public Health, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia and [4]Breakthrough Breast Cancer Research Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

Correspondence to: Dr A. Fancellu, Department of Clinical and Experimental Medicine, Unit of General Surgery 2, Clinica Chirurgica, University of Sassari, Viale San Pietro 43, 07100 Sassari, Italy (e-mail: afancel@uniss.it)

BJS 2015; **102**: 883–893

MRI and DCIS

- **9 Studien für diese Metaanalyse (7 Kohorten und 2 randomisierte Studien), die MRI im Rahmen der präoperativen Abklärung verwendet haben.**
- **4 Studien hatten sowohl DCIS als invasives Ca.**
- **In 4 Studien war BEO vorgesehen.**

Fancellu A et al, BJS, 102, 2015

MRI and DCIS

- **Adjusted odds ratios;**

  Estimates of the effect of preoperative MRI on surgical outcomes in patients with ductal carcinoma in situ;

Fancellu A et al, BJS, 102, 2015

MRI and DCIS

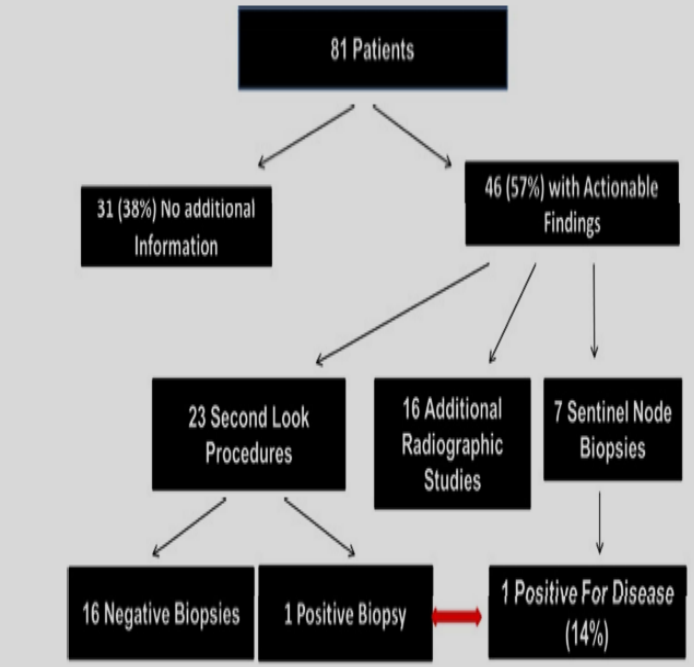
The present meta-analysis shows that preoperative MRI in women with DCIS is not associated with an improvement in surgical outcomes. MRI increases the initial rate of mastectomy, although the overall mastectomy rate is not significantly increased as a result of MRI. Importantly, this meta-analysis shows that preoperative MRI does not reduce the odds of having negative margins after BCS, nor does it reduce the odds of patients requiring reoperation for positive margins. On the basis of the collective evidence summarized in this meta-analysis, preoperative MRI does not improve the surgical treatment of women with DCIS of the breast.

MRI and DCIS

The True Impact of Breast MRI on the Management of In-Situ Disease: More is Not Better

Michael Lallemand MD*[1], Morgan Barron MD[2], Jason Bingham MD[3], Andrew Mosier MD[+4], Mark Hardin MD[5], Vance Sohn MD[6]

Over a seven year period, 93 patients were diagnosed with DCIS on percutaneous biopsy with no other indication for a breast MRI. Of these patients, 81 underwent an MRI preoperatively and comprised our patient cohort. Those that did not undergo an MRI were unable to do so either due to body habitus, anxiety, or the presence of an implantable pacemaker. In our patient cohort, 67 elected to undergo breast conservation therapy (BCT) and 14 decided to proceed with mastectomy. Of the BCT group, 8 required an additional procedure for positive margins (11.9%), four of whom chose to proceed with re-excision, while the remaining four were converted to mastectomy.



MRI and DCIS

The True Impact of Breast MRI on the Management of In-Situ Disease: More is Not Better

Michael Lallemand MD*[1], Morgan Barron MD[2], Jason Bingham MD[3], Andrew Mosier MD+[4], Mark Hardin MD[5], Vance Sohn MD[6]

Our data reveals that the routine use of MRI for DCIS did not change the overall clinical management in 88 of 89 patients (99%). Rather, it led to additional unnecessary studies and delayed time to definitive surgical therapy. Forty-six patients (57%) had a finding on MRI that prompted additional workup, including 17 additional biopsies, only one of which was positive.

At our institution, bilateral breast MRI is no longer routinely performed for patients being evaluated for DCIS. The impetus for this study was driven by the psychological distress that many patients felt by the time they needed to decide on a surgical treatment plan. Many felt overwhelmed and exhausted as they had already undergone numerous tests, biopsies, and delay to definitive therapy associated with the false positive findings on MRI. As stated, over half of the patients (57%) had a finding on MRI which prompted additional workup, including 16 negative biopsies. This study confirms that routine MRI is not useful to patients diagnosed with DCIS.

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Further Information

References

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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

- **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**

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

Ann Surg Oncol (2015) 22:3273–3281
DOI 10.1245/s10434-015-4740-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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, MD[1], Cristina Olcese, BS[1], Sujata Patil, PhD[2], Monica Morrow, MD, FACS[1], and Kimberly J. Van Zee, MS, MD, FACS[1]

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

Guidelines Breast
Version 2017.1

General Therapeutic Principles

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

Adjuvant treatment (radiotherapy, endocrine 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

	Oxford / AGO LoE	GR	
➢ Excisional biopsy (wire guided)	2b	B	++
➢ Bracketing wire localization in large lesions	5	D	+
➢ Specimen radiography	2b	B	++
➢ Intraoperative ultrasound (visible lesion)	3a	C	+/-
➢ Immediate re-excision for close margins (specimen radiography)	1c	B	++
➢ Intraoperative frozen section	5	D	- -
➢ Interdisciplinary board presentation	2b	C	++

Open biopsy in suspicious lesions (mammographical microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided

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Further Information

References

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Version 2017.1

Surgical Treatment for Histologically Proven DCIS II

	Oxford / AGO LoE / GR		
➢ Histologically clear margins (R0)	1a	A	++
➢ Multifocal DCIS: BCS 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	+
➢ BCS	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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Further Information

References

DCIS – Prognostic Factors for the Incidence of Ipsilateral Recurrence

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

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Further Information

References

FORSCHEN
LEHREN
HEILEN

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Version 2017.1

Radiotherapy Statements

- **Radiotherapy has no impact on survival** — **LOE 1a**
- **Radiotherapy reduces the risk of ipsilateral (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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Further Information

References

DCIS Radiotherapy

	Oxford / AGO LoE / GR		
Radiotherapy after:			
➢ **Breast conserving surgery (BCS)**	**1a**	**A**	**+***
➢ **Mastectomy**	**2b**	**B**	**- -**
Modality:			
➢ **Partial breast radiotherapy (PBI)**	**3a**	**D**	**--**
➢ **Hypofractionated radiotherapy regimens**	**2b**	**D**	**-/+****
➢ **Radiotherapy boost on the tumor bed**	**2b**	**D**	**--**
➢ **Women younger than 45-50 years**	**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**

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Further Information

References

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

Guidelines Breast
Version 2017.1

Goodwin A, Parker S, Ghersi 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.

Guidelines Breast
Version 2017.1

DCIS Postoperative Systemic Treatment - Statements

- **Postoperative endocrine treatment has no impact on survival** — **LOE 1a**
- **Postoperative endocrine treatment may have a small effect on ipsilateral invasive recurrences** — **LOE 1a**
- **Endocrine 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**

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Further Information

References

Cochrane Analysis
Tamoxifen after DCIS (all/with Radiation)

Guidelines Breast
Version 2017.1

Staley H, McCallum I, Bruce J.

Postoperative tamoxifen for ductal carcinoma in situ.

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

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Guidelines Breast
Version 2017.1

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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Further Information

References

Local Recurrence of DCIS after Tumorectomy w/o Irradiation

	Oxford LOE	/ AGO GR	
After radiation			
➢ **Simple mastectomy**	**3a**	**C**	**+**
+ SNB	**5**	**D**	**+**
➢ **Second tumorectomy** is followed by recurrences in up to 30 % of patients (NSABP B17)	**5**	**D**	**+/-**
No radiation after first tumorectomy			
➢ **Treatment like primary disease**	**3**	**C**	**++**

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

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Further Information

References

Ductal Carcinoma in Situ (DCIS) (2/24)

No further information

No references

Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

Mammographie
Vergrößerungsaufnahmen von Mikroverkalkungen
Steigerung der Detektionsrate von G1/G2 DCIS durch digitale Mammographie (versus konventionell)

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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
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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

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Klinische Untersuchung
Feinnadelpunktion / duktale Lavage
Interdisziplinäre Tumorboard-Präsentation

MRT and DCIS (4/24)

No further information

No references

MRI and DCIS (5/24-10/24)

No further information

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Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ (11/24-12/24)

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General Therapeutic Principles (14/24)

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Surgical Treatment for Histologically Proven DCIS I (15/34)

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Intraoperative Schnellschnittdiagnostik
Interdisziplinäre Tumorboard-Präsentation

Surgical Treatment for Histologically Proven DCIS II (16/24)

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Axilladissektion

DCIS – Prognostic Factors for the Incidence of Ipsilateral (17/24)

No further information

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Resektionsränder
Residualer tumorassoziierter Mikrokalk
Alter
Größe
Grading
Komedonekrose
Architektur

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(mod.) Van Nuys Prognose Index und MSKCC Nomogramm

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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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DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

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Intrinsische Subgruppen (Luminal A,B, HER+, triple negativ)

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Radiotherapy Statements (18/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

See next slides

DCIS Radiotherapy (19/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

References:

Radiotherapie nach:
Brusterhaltender Operation (BEO) (gesamte Brust, WBI)

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Bei Patientinnen unter 45-50 Jahren

Cochrane Analysis – Radiation after Surgery (20/24)

No further information

No references

DCIS Postoperative Systemic Treatment - Statements (21/24)

No further information

References:

See next slides

Cochrane Analysis - Tamoxifen after DCIS (all/with radiation) (22/24)

No further information

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DCIS Postoperative Systemic Treatment (23/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung

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Tamoxifen (nur ER+, nur BET)

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<u>AI (wenn postmenopausal und Kontraindikationen gegen Tamoxifen)</u>
<u>Andere endokrine Optionen Trastuzumab (nur HER2+)</u>

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Local Recurrence of DCIS after Tumorectomy w/o Irradiation (24/24)

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

Guidelines Breast
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Breast Cancer Surgery
Oncological Aspects

START

Breast Cancer Surgery
Oncological Aspects

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- **Versions 2002–2016:**
  Bauerfeind / Blohmer / Böhme / Brunnert / Costa / Fersis / Gerber / Hanf / Janni / Junkermann / Kaufmann / Kühn / Kümmel / Nitz / Rezai / Simon / Solomayer / Thill / Thomssen / Untch

- **Version 2017:**
  Kühn / Rezai

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Version 2017.1

Breast Cancer Surgery
Oncological Aspects

AGO: ++

Surgery is 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.

Pretherapeutic Assessment

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	Oxford / AGO LoE	GR	
➢ Palpation	5	D	++
➢ Mammography	2b	B	++
➢ Ultrasound (breast & axilla)	2b	B	++
➢ Minimal invasive biopsy*	1c	A	+
➢ MRI**	1c	B	+/-

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*** 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 3-4, C, D and invasive lobular cancer , suspicion of multifocal or multicentric disease)

Perioperative Staging

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	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	-

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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	2b	C

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Breast Conservation: Surgical Technical Aspects

	Oxford / AGO LoE	GR	
➢ **Non-palpable lesion**			
➢ Wire guided localisation	2b	B	++
➢ Radionuclide guided localisation	2b	B	+/-
➢ Specimen radiography or ultrasound	2b	B	++
➢ **Tumor-free margins required** (also in unfavorable biology „no cells on ink“ are enough)	2a	A	++
➢ **Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)**	1c	B	++
➢ **Re-excision required for involved margins (paraffin section)**	3b	C	+
➢ **Therapeutic stereotactic excision alone**	4	D	- -
➢ **Ultrasound guided surgery to prevent re-excision**	1a	A	+/-
➢ **Intraop. margin evaluation with margin probe**	1b	A	+/-

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Breast Conservation Surgery (BCS)

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	Oxford / AGO LoE / GR		
➢ **Multicentricity**	2b	B	+/-
➢ **Positive microscopic margins after repeated excision**	2b	B	- -
➢ **Inflammatory breast cancer**	2b	B	- -

Surgery after neoadjuvant chemotherapy go to chapter „neoadjuvant chemotherapy“

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Axillary Lymph Node Dissection I

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	Oxford / AGO LoE	GR	
Axillary lymph node dissection (>=10 LN)			
➢ To improve survival	3	D	-
➢ For staging	3	A	-
➢ For local control	2a	A	+/-
Axillary lymph node dissection			
➢ DCIS	2b	B	- -
➢ If SLNB is possible	1a	A	- -
➢ SN + (cT1/2 cN*0; < 3 SN +, BCS + tangential radiation field, no subsequent axillary radiation, adequate systemic therapy)	1b	B	+/-
➢ SN + (mic)	1b	A	-
➢ SN (i+)	2b	B	- -
➢ SN + mastectomy (no radiotherapy of the chestwall)	1b	B	+
➢ SN+ mastectomy (radiotherapy of the chestwall)			
➢ Only if T1, T2 and 1-2 pos. SLN	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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Axillary Intervention Before or After NACT

Oxford / AGO
LoE / GR

SLNB before or after NACT in cN0						
SLNB before NACT **SLNB after NACT**					**2b** **2b**	**B** **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**	**5** **2b** **3**	**D** **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)**	**ycN0** **ycN+**		**SLNB alone*** **ALND** **ALND**	**2b** **2b** **2b**	**B** **B** **B**	**+/-** **+** **++**

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Improvement of the False-Negative Rate of SLNB after NACT in Patients with (cN+) (FNA/CNB)

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	Oxford / AGO LoE / GR		
➢ Removal of > 2 SLNs	3b	C	+/-
➢ Combined tracer	3b	C	+/-
➢ IHC and serial sections	2b	C	+/-
➢ LN localisation	3b	C	+/-

Sentinel Lymph Node Biopsy (SLNB): Indications I

	Oxford / AGO LoE / GR		
➢ Clinically (cN0) / sonographically neg. axilla	1b	A	++
➢ Add. FNA/CNB of LN (clinical/sonogr. suspicious) 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	+

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Further Information

References

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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**

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References

Sentinel Lymph Node Excision (SNE): Marking

Guidelines Breast
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	Oxford / AGO LoE	GR	
➢ ^{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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Further Information

References

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SPIO: Superparamagnetic Iron Oxide

* Study participation recommended

Guidelines Breast
Version 2017.1

Procedure after Neoadjuvant Therapy

	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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References

Adjuvant Therapy after Primary Surgery

	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 Information

References

Breast Cancer Surgery Oncologic Aspects (2/16)

Further information and references:

Update Januar 2017

Screened data bases: Pubmed 1998 - 2016, ASCO 2016, SABCS 2016, ESMO 2016, EBCC 2016
Screened consensus conference:

- Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013.
  Ann Oncol. 2013 Sep;24(9):2206-23. doi: 10.1093/annonc/mdt303. Epub 2013 Aug 4.

Cochrane library:
- http://onlinelibrary.wiley.com/cochranelibrary/search

Breast Cancer Surgery Oncologic Aspects (3/16)

No further information

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No further information

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Pre-operative staging (5/16)

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Breast Conservation Surgery (8/16)

No further information

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Axillary Lymph Node Dissection I (9/16)

No further information

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

No further information

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Axillary Intervention Before or After NACT (11/16)

No further information

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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 Therapy (15/16)

No further information

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Statement: clip marking

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Ajuvant Therapy after Primary Surgery (16/16)

No further information

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Statement AI concurrent with radiotherapy

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Guidelines Breast
Version 2017.1

Oncoplastic and Reconstructive Surgery

START

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Oncoplastic and Reconstructive Surgery

- **Versions 2002–2016:**
  Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Fersis / Gerber/ Hanf / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Thomssen

- **Version 2017:**
  Kümmel / Solbach (in consens with AWOGyn)

Definition of Oncoplastic Surgery

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

Oncoplastic Breast Conserving Surgery

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Version 2017.1

	Oxford / AGO LoE	GR	
➢ Tumor adapted reduction mammaplasty	2a	B	+
➢ Local flap techniques	2a	B	+
➢ Partial mastectomy with tissue transfer	3b	B	+/-
➢ Oncological safe	2a	B	
➢ Complication rate comparable with lumpectomy	2a	B	

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Algorithm of Breast Reconstruction

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Patient wishes to undergo breast reconstruction
N.B.: Habitus, breast volume, wishes

No postmastectomy radiotherapy

SSM/NSM and implantation
or
MRM + tissue expander → Implantat

Postmastectomy radiotherapy indicated

Mastectomy
→Radiotherapy
→Delayed autologous reconstruction

Not suitable for autologous reconstruction
E.g. too little subcutaneous fat, wishes of patient

Prosthesis reconstruction
Radiotherapy
N.B.: Increased complication rate, particularly capsular fibrosis

To be discussed in individual cases:
Immediate autologous reconstruction
N.B.: Increased fibrosis rate

Delayed prothesis reconstruction
N.B.: Increased complication rate

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Breast Reconstruction
General Considerations

AGO: ++

- **Counceling 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, bilateral mastectomy

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References

Timing of Reconstruction

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	Oxford / AGO LoE	GR	
➢ **Immediate BR**	3b	B	++
➢ Mandatory: SSM / NSM			
➢ Avoidance of a postmastectomy syndrome			
➢ **Delayed BR**	3b	B	++
➢ No interference with adjuvant procedures (CHT, RT)			
➢ Disadvantage: loss of skin envelope			
➢ **„Delayed-immediate“ BR**	3b	B	+/-

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Timing of Implant Based Reconstruction and Radiotherapy

Guidelines Breast
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	Oxford / AGO LoE	/ GR	
➢ **Implant reconstruction (IR)**	2a	B	+
➢ **IR without radiotherapy (RT)**	2a	B	++
➢ **IR prior to RT / following PBRT (higher complication rate)**	2a	B	+
➢ **IR following MX and RT**	2b	B	+/-
➢ **IR following Mx for local relapse after BCT**	2a	B	+/-
➢ **Periop. antibiotic therapy (at least 24 h)**	2b	B	+

*MX = Mastektomie

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Tissue Replacement Techniques and Meshes

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	Oxford / AGO LoE	GR	
➢ **Autologous tissue (e.g. autodermal graft, LDF*)**	3b	C	+#
➢ **Acellular dermal matrix (ADM)**	2b	B	+#
➢ **Synthetic mesh**	2b	B	+#

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* LDF = Latissimus dorsi flap

Participation in register study recommended

Lipotransfer

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	Oxford / AGO LoE / GR		
➢ Lipotransfer after MX and breast reconstruction	2a	B	+
➢ Lipotransfer after breast-conserving therapy	2a	B	+
➢ Autologous adipose derived stem cells (ASCs)-enriched fat grafts	5	D	-

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Postmastectomy Pedicled Reconstruction

	Oxford / LoE	AGO / 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 (more fibrosis, more wound healing problems, more liponecrosis)**	**2a**	**B**	**+/-**

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Free Tissue Transfer

	Oxford LoE	AGO GR	
Free tissue transfer			
➢ **DIEP-flap**	2a	B	+
➢ **Free TRAM-flap**	2a	B	+
➢ **SIEA-flap**	3a	C	+/-
➢ **Gluteal Flaps (SGAP- / IGAP-flap/FCI)**	4	C	+/-
➢ **Free gracilis flap (TMG)**	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 reoperation rate
- Pre-reconstruction RT increases rate of vascular complications

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Pedicled vs. Free Tissue Transfer

	Oxford LoE	AGO GR	
➢ **Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used**	3a	A	++
➢ **Autologous abdominal-based reconstructions have the highest satisfaction in all patient groups without any difference**			
➢ **Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration in all flap techniques**			

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Flap-Implant Combination

	Oxford LoE	/ GR	AGO
LDF* + implant	**2b**	**C**	**+**
➢ **IR following RT**	**3b**	**C**	**+**
➢ **IR prior to RT**	**5**	**D**	**-**
Other flaps + implant	**5**	**C**	**+/-**

Advantages:

- TRAM: staged procedure preferable
- Improved implant coverage
- Suitable for radiated tissue

Disadvantage:

- Muscle contraction (LDF)

* LDF = Latissimus dorsi flap

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Further Information

References

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

	Oxford LoE	/ GR	AGO
➢ **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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Risk Reducing Bilateral Mastectomy in Healthy Women (RRBM)

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	Oxford / AGO LoE	/ GR	
➢ RRBM reduces breast cancer incidence	1b	A	++
➢ RRBM in deleterious BRCA1/2 mutation	2a	B	+*
➢ RRBM in high risk situation without BRCA 1/2 mutation (individual decision depending on personal-family history and mutational status – e.g. high and moderate risk genes, Hodgkin lymphoma)	4	D	+/-*
➢ High risk and no BRCA counselling in specialized centre*	5	D	- -
➢ Non-directive counselling prior to RRBM	2b	B	++*
➢ RRBM should be considered with other prophylactic surgical options incl. bilateral salpingoophorectomy (BSO)	2a	A	++*
➢ Further need for education of physicians regarding possibilities and advantages of RRBM	1b	A	++

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

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Types of Risk Reducing (bilateral) Mastectomy (RRBM)

	Oxford / AGO LoE	/ GR	
Risk Reducing Mastectomy reduces breast cancer incidence; bc-spec mortality reduction likely			
➢ **Simple mastectomy**	2b	B	+
➢ **RRBM by SSM***	2b	C	+
➢ **RRBM by NSM* (NAC# sparing)**	2b	C	+
➢ **Contralateral prophylactic MX**	4	C	+/-

* SSM / NSM: Skin-/Nipple-Sparing Mastectomy
# NAC: Nipple-Areola-Complex

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Further Information

References

Oncoplastic and Reconstructive Surgery (2/18)

Further information and references:

Pubmed 2003 - 2016
Cochrane data base (z.B. Cochrane Breast Cancer Specialised Register)
Suchbegriffe: breast reconstruction; … AND random allocation, … AND cohort study

Einteilung in EBM-Grade nach

Jeremy Howick, Iain Chalmers, Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, and Hazel Thornton. "The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document)". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Verwendete Guidelines zu Diagnostik und Therapie des Mammakarzinoms:

National Institute of Health (NIH) – National Cancer Institute:
http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/
American Association of Clinical Oncology (ASCO) and Technology Assessments: http://www.asco.org/portal/site/ASCO/menuitem. (Practice Guidelines),
Canadian Medical Association (CMA): http://www.cmaj.ca/cgi/content/full/158/3/DC1
NCCN 2016
Regeln zur Überarbeitung der AGO Empfehlungsdias_Stand 04.08.2016

Definition of oncoplastic surgery (3/18)

Further information:

Aesthetics must play a key role in the surgery of the breast in order to avoid deformities which could have a negative impact on a patient`s self esteem irrespective of age. With the help of oncoplastic surgery free margins due to wide excisions of malignant tumors are possible without compromising the shape of the breast thus preserving physical integrity. As a result oncoplastic surgery plays an integral role in the primary surgical treatment of BC.

No references

Oncoplastic breast conserving surgery (4/18)

No further information

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Algorithm of Breast Reconstruction (5/21)

No further information

References:

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Breast Reconstruction - General Considerations (6/18)

No further information

References:

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Postmastectomy Reconstruction (7/18)

No further information

References:

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Timing of Reconstruction (8/18)

No further information

References:

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

No further information

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Types of Risk Reducing Mastectomy (18/18)

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Guidelines Breast
Version 2017.1

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

START

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Guidelines Breast
Version 2017.1

- **Versions 2002–2016:**

  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 2017:**

  Hanf / Lux

Guidelines Breast
Version 2017.1

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 doubtfully responsive**
≥10% pos. cells:	**endocrine responsive**

Status unknown: **endocrine responsive**

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References

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Guidelines Breast
Version 2017.1

Oxford / AGO
LoE / GR

Assessment of menopausal status

- **Menstruation history** **+**
- **FSH, E2** **++**

Guidelines Breast
Version 2017.1

Adjuvant Endocrine Therapy

Standard therapy for endocrine responsive / doubtfully responsive tumors:

	Oxford / AGO LoE / GR
➢ **Endocrine therapy**	**1a A ++**
➢ **Chemotherapy followed by endocrine therapy** (dependent on individual risk and tumor biology)	**1a A ++**

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Adjuvant Endocrine Therapy

	Oxford / AGO LoE / GR		
➢ **Endocrine responsive & doubtfully 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 ++

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- **Adjuvant endocrine therapy is devided into initial therapy (years 0-5) and extended adjuvant therapy (EAT, years 6-15).**
- **Standard treatment duration is 5 years.**
- **Extended treatment should be considered based on individual benefits and risks.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability and risks.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than to stop.**
- **AI as first treatment in postmenopausal patients especially in cases of high risk and lobular cancers.**
- **To date, there is no validated biomarker that identifies patients for early versus late recurrence.**

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Premenopausal Patients
Adjuvant Endocrine Therapy

	Oxford LoE	/ GR	AGO
➢ Tamoxifen* 5 -10 years	1a	A	++
➢ GnRH alone (only, if relevant contraindication for Tam)	1a	B	+
➢ In patients with ovarian function (within 8 mon.) after adjuvant chemotherapy:			
➢ # OFS (ovarian function suppression) 5 years + Tam 5 years	1b	B	+/-
➢ in patients < 35 y.	1b	B	+
➢ # OFS 5 years + AI 5 years	1b	B	+/-

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Further Information

References

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* Treat as long as tolerable and premenopausal

\# Increased side effects may impair compliance. Higher compliance to TAM alone ist more effective, than addition of GNRH or treatment with GNRH+AI and impaired compliance.

Postmenopausal Patients
Initial Adjuvant Endocrine Therapy
(Years 0-5)

	Oxford / AGO LoE	GR	
➢ **AI for first 5 years**	1a	A	++
➢ **Especially in case of lobular cancer**			
➢ **High risk of recurrence**			
➢ **Sequential therapy for first 5 years**			++
➢ **Tam (2-3 yrs.) followed by AI to complete 5 years**	1a	A	
➢ **AI (2-3 yrs.) followed by Tam to complete 5 years**	1b	C	
➢ **Tamoxifen 20 mg/d for 5 yrs.**	1a	A	+

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References

Postmenopausal Patients
Extended Adjuvant Endocrine Therapy
(Years 6-10)

	Oxford / AGO LoE	GR	
➢ 2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy	1b	B	+
➢ 5 years Tamoxifen after 5 years Tamoxifen (in case of higher risk)	1a	A	++
➢ After 2 - 5 years Tamoxifen AI for 2.5 - 5 years	1a	B	++
➢ After initial therapy with AI further prolongation of endocrine therapy with AI*			
➢ high risk and good tolerabilty of the AI	1b	B	+
➢ low risk, poor tolerabilty of the AI	1b	B	-

* Up to date, no impact on OS

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Further Information

References

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

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	Oxford / AGO LoE / GR		
➢ **For ovarian function protection**			
CT + GnRHa (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)	1a	B	+
➢ **Fertility preservation counselling**	4	C	++
➢ **Fertility preservation using assisted reproduction therapy (ART) (further information www.fertiprotect.de)**	4	C	+

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Further Information

References

TEXT /SOFT Joint Analysis

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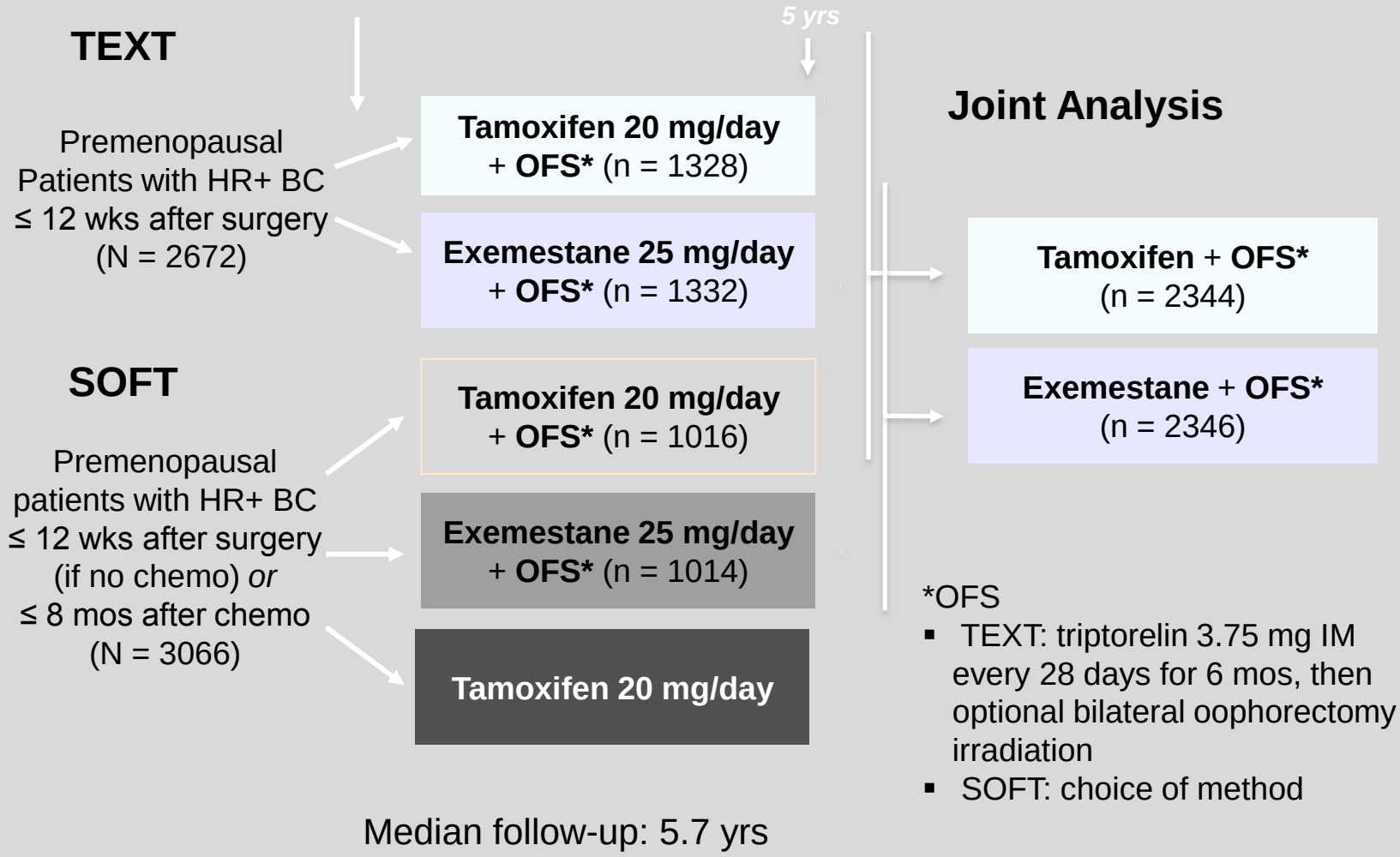

Median follow-up: 5.7 yrs

*OFS
- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

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Further Information

References

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Nach Pagani O, et al. N Eng J Med, 371(2) 2014

Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy)

- **In Soft-EST: Exe + OFS: E2, E1, E1-Sulfate - levels were significantly lower than in pats. with Tam + OS**
- **66% of premenopausal pats. on Exe + OFS had profound persistent suppression of E2 etc. for 12 months.**
- **However, 34% had an E2 level greater than menopausal threshold at least once, 17% at all time-points:**
  - **These patients were more likely younger than 35 y; chemo-naïve; had higher BMI**
  - **Importantly:** Combining ABCSG-12, SOFT, and TEXT studies, **showed 65 fewer DFS events** (HR 0.89, 95% CI 0.57–1.39) **but 30 more deaths** for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, P = 0.12, s = 0.03, heterogeneity, P = 0.18).
- **Hence the question arises, whether incomplete ovarian suppression led to this discrepancy**

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Further Information

References

Ovarian Suppression in Combination Endocrine Adjuvant Therapy in Premenopausal Women with Early Breast Cancer

Chlebowski RT, Pan K, Col NF, Breast Cancer Res Treat
DOI 10.1007/s10549-016-4024-4

“Conclusion: Given the discordance between DFS and OS and inconsistent estrogen suppression with ov. suppr. plus AI, adding AI to ov. suppr. as adjuvant therapy in premenopausal women is premature.“

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Further Information

References

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10 yrs versus 5 yrs Breast Cancer Mortality in ER+
Rate ratio per period in aTTom and ATLAS
5 yrs. vs. 10 yrs Tamoxifen

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

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

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Version 2017.1

Upfront Therapies
Overview

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Initial Therapy (years 1-5)

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 Hyperlypidaemia A>E	Randomization for Celecoxib cancelled
Meta-analysis EBCTCG	EBCTCG 2015		5 y. AI vs. 2-3 y. tam → AI to y. 5 vs. 5 y. Tam	31920		10 y. gain recurrence rate 5 y. AI vs. 5 y. Tam 3,6%, p<0,00001	10 y. gain OS 5 y. AI vs. 5 y. Tam 2,1%, p<0,009		
						10 y. gain recurrence rate 5 y. AI vs. 2-3 y. Tam → AI to y. 5 0,7%, p<0,045	10 y. gain OS 5 y. AI vs. 2-3 y. Tam → AI to y. 5 1,1%, p<0,11		
						10 y. gain recurrence rate 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 2,0% p<0,0001	10 y. gain OS 2-3 y. Tam → AI to y. 5 vs. 5 y. Tam 1,5% , p<0,01		

A anstrozole; 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 advesrse 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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Further Information

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5 Years of Aromatase Inhibitor versus 5 Years of Tamoxifen

Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.
Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
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5 Years of Aromatase Inhibitor versus Tamoxifen to Years 2-3 Followed by AI to year 5

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
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Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
Epub 2015 Jul 23.

Tamoxifen to Years 2-3 Followed by AI to Year 5 versus 5 Years of Tamoxifen

Guidelines Breast
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Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R.
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Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1.
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Guidelines Breast
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Upfront Monotherapy: Meta-analyses of DFS and OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
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Upfront Sequential Therapy: Meta-analyses of DFS

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Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
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Epub 2016 Feb 18.

Guidelines Breast
Version 2017.1

Upfront Sequential Therapy: Meta-analyses of OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
Breast. 2016 Apr;26:106-14.
doi: 10.1016/j.breast.2016.01.006.
Epub 2016 Feb 18.

Upfront sequential therapy: Meta-analyses of DFS and OS

Guidelines Breast
Version 2017.1

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials.
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doi: 10.1016/j.breast.2016.01.006.
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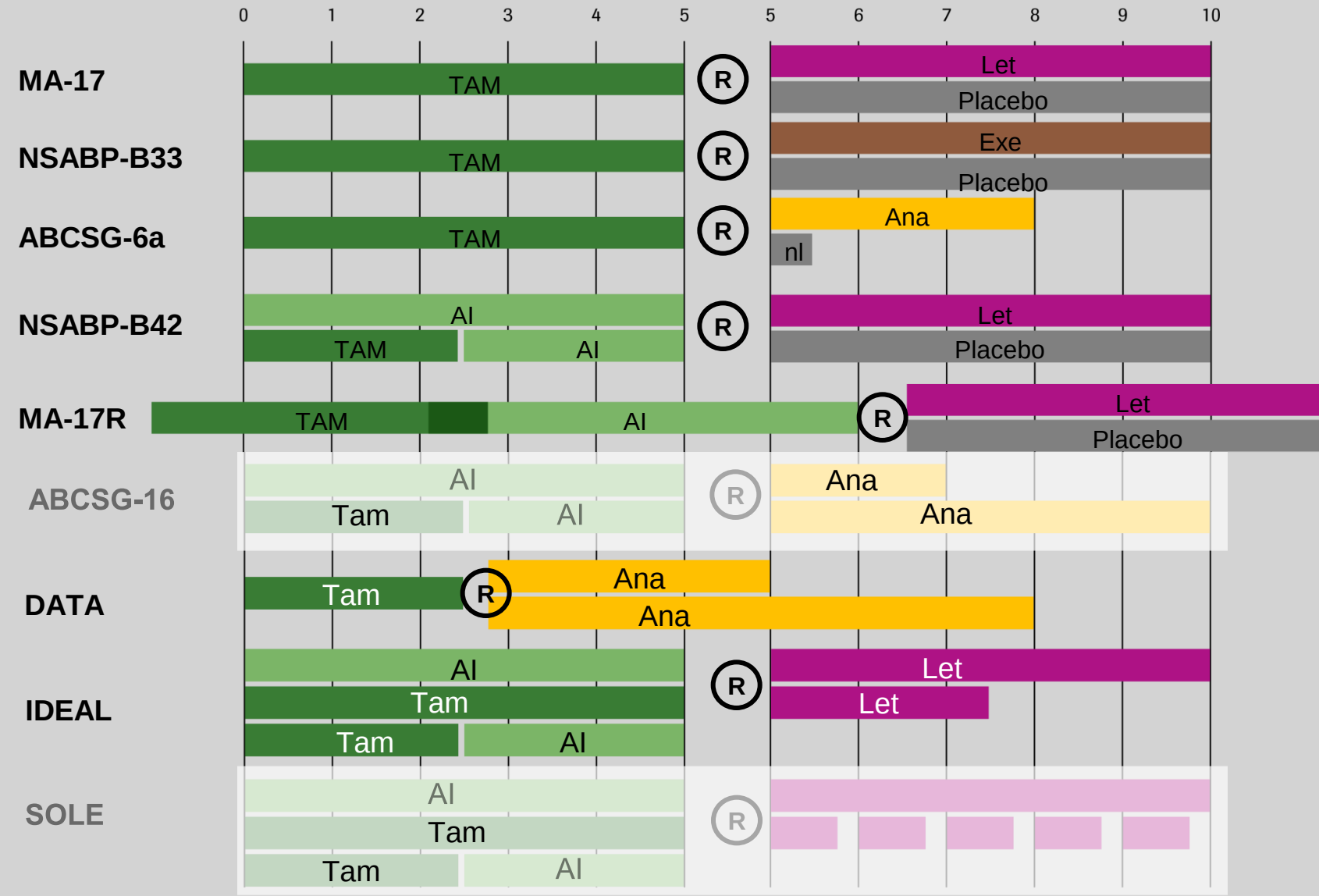
Extended Endocrine Therapies

Gnant M. et al., SABCS, 2016 (S1-06, Discussion)



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Further Information

References

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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy I

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
ECOG	Tomey 1996	193	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	RFS: 85% vs. 73% (p=0.10) OS: 86% vs. 89% (p=0.52)
Scottish	Stewart 1996	342	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Events: 60 vs. 49 EFS HR: 1.27 (0.87-1.85)
NSABP B-14	Fisher 2001	1142	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	DFS: 78% vs. 82% (p=0,03) OS: 91% vs. 94% (p=0,07)
ATLAS	Davies 2013	6846	Prem./postm.	Tamoxifen	Tamoxifen vs. placebo	Recurrence: 617 vs. 711 (p=0,01) OM: 639 vs. 722 (p=0,01)
aTTOM	Gray 2013	6953	Prem./postm.	Tamoxifen	Tamoxifen vs. no therapy	Recurrence: 580 vs. 672 (p=0.003) OM: 849 vs. 910 (p=0.1)
MA.17	Goss 2005	5187	Postm.	Tamoxifen	Letrozole vs. placebo	DFS: HR 0.68 (0.55-0.83; p=0.001) OS: HR 0.98 (0.78-1.22; p=0.85)
NSABP B-33	Mamounas 2008	1598	Postm.	Tamoxifen	Exemestane vs. placebo	DFS: 91% vs. 89% (p=0.07) RFS: 96% vs. 94% (p=0.004)
ABCSG-6a	Jakesz 2007	856	Postm.	Tamoxifen	Anastrozole vs. placebo	Recurrence: 30 vs. 56, HR 0.64 (0.41-0.99: p=0.047)
Meta-analysis	Petrelli 2013	29138	Prem./postm.	Tamoxifen	Fixed duration (5 years) with an extended course of endocrine therapy vs. no therapy	RFS OR: 0.72 (0.56-0.92; p=0.01) BCSS OR: 0.78 (0.69-0.9; p=0.0003) OS OR: 0.89 (0.80-0.99; p=0.03)

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival

Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy II

Trial	Source	Patient number	Population	Upfront therapy	Trial Arms	Reported outcomes
LATER	Zdenkowski 2016	360	Postm.	≥ 4 years of endocrine therapy (11.7% AI, 50.3% Tam, 38.0% other)	5 y. letrozole vs. observation	Breast cancer recurrence difference: 8.4% (3.8%-13.0%), p=0.0004
MA17R	Goss 2016	1918	Postm.	5 years of any other AI with or without prior tamoxifen	Letrozole vs. placebo	DFS: 95% vs. 91% (HR for disease recurrence or occurrence of contralateral breast cancer: 0.66; p=0.01) OS: 93% vs. 94% (HR: 0.97; p=0.83)
IDEAL	Blok 2016	1824	Postm.	5 years of tamoxifen, AI or tamoxifen → AI	Letrozole 2.5 vs. 5 years	DFS HR: 0.88 (0.64-1.21; p=0.43) 5-year DFS: 88.4 vs. 87.9% OS HR: 1.09 (0.70-1.70)
DATA	Tjan-Heijnen 2016	1912	Postm.	Tamoxifen 2-3 years	Anastrozole 6 vs. 3 years	DFS HR: 0.79 (0.62-1.02; p=0.07) 5-year DFS: 83.1 vs. 79.4 OS HR: 0.91 (0.65-1.29)
NSABP B-42	Mamounas 2016	3923	Postm.	AI or tamoxifen → AI 5 years	Letrozole vs. placebo	DFS HR: 0.85 (0.73-0.999; p=0.048*) * did not reach statistical significance level of 0.0418

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival

Conclusion for Possible Therapy Decision Extended Endocrine Therapy

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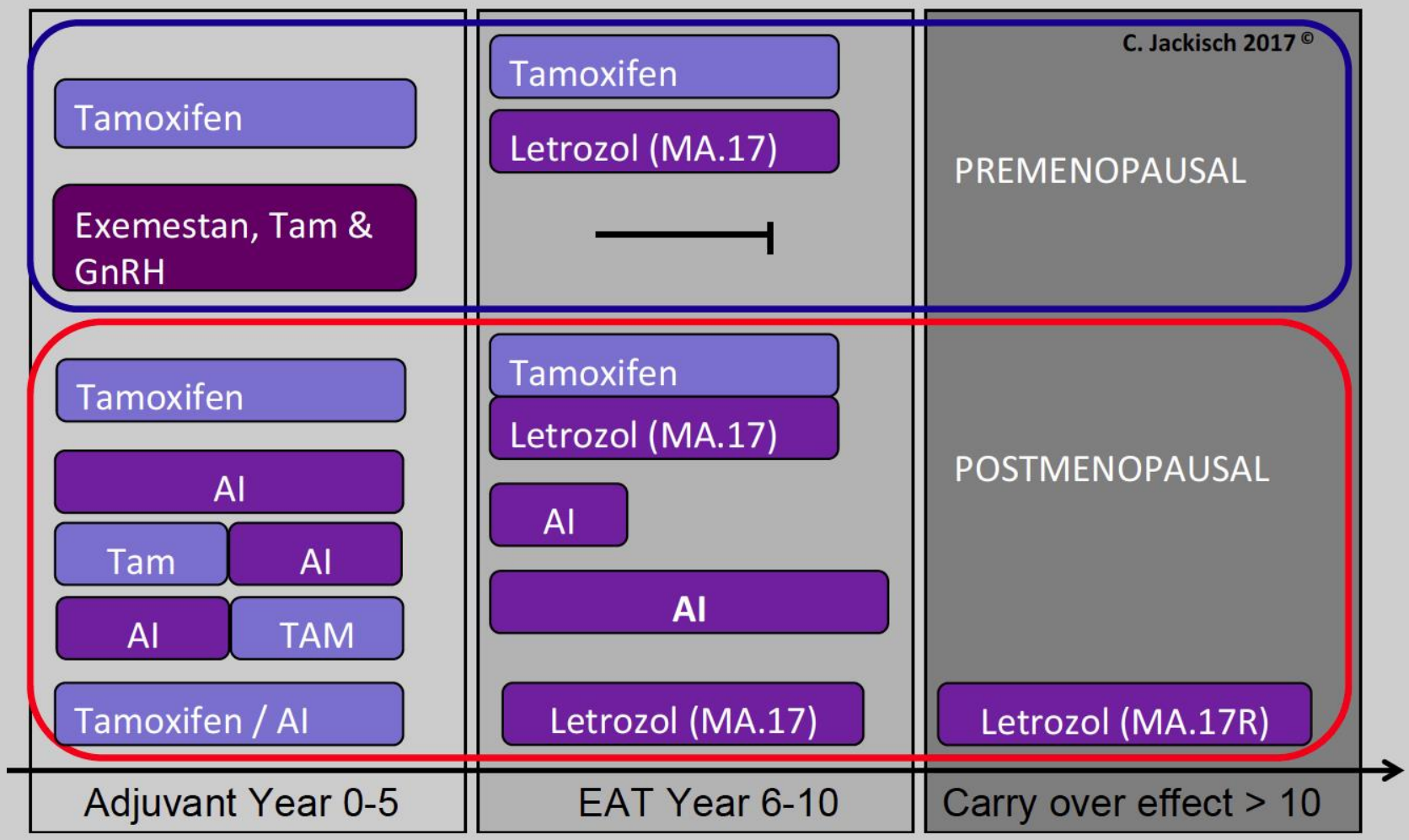
- **After 2 - 5 years tamoxifen**
  → add aromatase inhibitor for 2,5 to 5 years.
- **After initial aromatase inhibitor therapy consider carefully:**
  - **further AI therapy:**
    - **up to now well tolerated AI therapy,**
    - **good bone health,**
    - **younger age,**
    - **high risk by clinopathological factors,**
    - **node positive disease.**

nach Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

Possible Ways



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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/29)

No further information

No references

Assessment of Steroid Hormone Receptor Status (3/29)

No further information

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Adjuvant Endocrine Therapy – Assessment of Menopausal Status (4/29)

No further information

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Adjuvant Endocrine Therapy (5/29)

No further information

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General Principles in Adjuvant Endocrine Therapy AGO ++ (7/29)

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Discussant General Session 1, Dec. 7th, SABCS 2016, https://watch.ondemand.org/OnlinePlayer/228

Premenopausal Patients - Adjuvant Endocrine Therapy (8/29)

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Tamoxifen 5-10 yrs. 1a A ++

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GnRHa alone 1a B +

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In patients with ovarian function (within 8 mon.) after adjuvant chemotherapy:
OFS (ovarian function suppression) 5 years + Tam 5 years 1b B +/-

- in patients < 35 y. 1b B +

OFS 5 years + AI 5 years 1b B +/-

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Postmenopausal Patients Initial Adjuvant Endocrine Therapy (years 0-5) (9/29)

No further information

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AI for first 5 years 1a A ++
Especially in case of lobular cancer
High risk of recurrence

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Sequential therapy for first 5 years	++	
Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A
AI (2-3 yrs.) followed by Tam to complete 5 years	1b	C

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Tamoxifen 20 mg/d for first 5 yrs.	1a	A	+

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Postmenopausal Patients Extended Adjuvant Endocrine Therapy (years 6-10) (10/29)

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5 years Tamoxifen after 5 years Tamoxifen (in case of higher risk) 1a A ++

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After 2 - 5 years Tamoxifen AI for 2.5 - 5 years 1a B ++

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After initial therapy with AI further prolongation of endocrine therapy with AI*
high risk and good tolerabilty of the AI 1b B +
low risk, poor tolerabilty of the AI 1b B -

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT) (11/29)

No further information

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See chapter 25 Gynecological problems

TEXT /SOFT Joint Analysis (12/29)

No further information

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Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy) (13/29)

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Ovarian Suppression in Combination Endocrine Adjuvant Therapy in Premenopausal Women with Early Breast Cancer (14/29)

No further information

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10 yrs versus 5 yrs Breast Cancer Mortality in ER+ - Rate ratio per period in aTTom and ATLAS - 5 yrs. vs. 10 yrs Tamoxifen (15/29)

No further information

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Upfront therapies - Overview (16/29)

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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Initial Therapy (17/29)

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5 Years of Aromatase Inhibitor versus 5 Years of Tamoxifen (18/29)

No further information

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5 Years of Aromatase Inhibitor versus Tamoxifen to Years 2-3 Followed by AI to Year 5 (19/29)

No further information

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Tamoxifen Years 2-3 Followed by AI to Year 5 versus 5 Years of Tamoxifen (20/29)

No further information

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Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, Bliss J, Boccardo F, Coates A, Coombes RC, Cuzick J, Dubsky P, Gnant M, Kaufmann M, Kilburn L, Perrone F, Rea D, Thürlimann B, van de Velde C, Pan H, Peto R, Davies C, Gray R. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-52. doi: 10.1016/S0140-6736(15)61074-1. Epub 2015 Jul 23.

Upfront Monotherapy: Meta-analyses of DFS and OS (21/29)

No further information

References:

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Upfront Sequential Therapy: Meta-analyses of DFS (22/29)

No further information

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Upfront Sequential Therapy: Meta-analyses of OS (23/29)

No further information

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Upfront sequential therapy: Meta-analyses of DFS and OS (24/29)

No further information

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Extended Endocrine Therapies (25/29)

No further information

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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy I (26/29)

No further information

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Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy II (27/29)

No further information

References:

See 26/29.

Conclusion for possible therapy decision extended endocrine therapy (28/29)

No further information

References:

1. Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

Possible Ways (29/29)

No further information

No references

Guidelines Breast
Version 2017.1

Adjuvant Cytotoxic and Targeted Therapy

START

Adjuvant Cytotoxic and Targeted Therapy

Guidelines Breast
Version 2017.1

- **Version 2002:**
  Möbus / Nitz
- **Versions 2003–2016:**
  Harbeck / Jackisch / Janni / Loibl / Lux / von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Schütz / Solomeyer / Stickeler / Thomssen / Untch
- **Version 2017:**
  Dall / Stickeler

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Further Information

References

Guidelines Breast
Version 2017.1

Subtype-specific General Systemic Strategies

	AGO
If chemotherapy is indicated due to tumor biology, consider systemic treatment before surgery (neoadjuvant)	++
HR+/HER2- and "low risk":	
➢ **Endocrine therapy without chemotherapy**	++
HR+/HER2- and "high risk"	
➢ **Conventionally dosed AT-based chemotherapy**	++
➢ **Dose dense & escalated in case of high tumor burden**	+
➢ **Followed by endocrine therapy**	++
HER2+	
➢ **Trastuzumab (plus Pertuzumab neoadjuvant) 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**	+

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References

Adjuvant Chemotherapy without Trastuzumab: Overview

Guidelines Breast
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	Oxford LoE	AGO 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	++
➢ **Low dose maintenance chemo**	1b	B	-

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Further Information

References

Colleoni et al., J Clin Oncol 2016, 34: 3400-8

rand. phase 3-study of IBCSG: trial 22-00

n = 1086 pat., HR neg.,

DFS as primary endpoint

OP -> adj. CT -> R -> Cyclophos. 50 mg p.o. cont. plus
Mtx 2.5 mg 2 x tgl. p.o. d 1 + 2, q1w
versus
control (nil)

Results:
FU 6.9 yrs.,

n.s. DFS difference,

more side effects (14% WHO3/4) in the CM-arm

Recommended Regimens for Adjuvant Chemotherapy

Guidelines Breast
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Further Information

References

		Oxford / AGO LoE	GR	
Anthracycline / taxane based regimen				
➢ *EC → P_w	$E_{90}C$ q3w x 4 → P_{80} qw1 x 12	1b	B	++
➢ AC → P_w	$A_{60}C$ q3w x 4 → P_{80} qw1 x 12	1b	A	++
➢ AC → D	$A_{60}C$ q3w x 4 → D_{100} qw3 x 4	1b	A	++
➢ *EC → D	$E_{90}C$ q3w x 4 → D_{100} qw3 x 4	1b	B	++
➢ DAC	$D_{75}A_{50}C$ q3w x 6	1b	A	++
Anthracycline-free regimen				
➢ DC	D_{75} C_{600} x4	1b	B	+
➢ Pac mono	P_{80} q1w x 12	1b	B	+/-
➢ CMF		1a	A	+/-

*** Extrapolated from doxorubicin trials**

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

	Oxford LoE	/ GR	AGO
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	++

* Extrapolated from doxorubicin trials

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Adjuvant Chemotherapy
Other Drugs

	Oxford LoE	/	AGO GR	
➢ Capecitabine containing regimen in TNBC	1a		B	+/-
➢ Platinum containing regimen in TNBC	5		D	+/-
➢ 5- Fluorouracile added to EC/AC	1b		A	- -

Adjuvant Treatment with Trastuzumab I

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	Oxford LoE	/	AGO GR	
➢ **Node-positive disease**	1a		A	++
➢ **Node-negative disease (whenever chemotherapy is considered as adequate)**				
➢ **> 10 mm**	1a		A	++
➢ **> 5–10 mm**	2b		B	+
➢ **≤ 5 mm**	2b		B	+/-

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References

Adjuvant Treatment with Trastuzumab II

Guidelines Breast
Version 2017.1

	Oxford LoE	/ AGO GR	
Start of treatment			
➢ Simultaneously with taxanes	1a	A	++
➢ Sequentially up to 3 months after chemotherapy	1b	B	+
Duration			
➢ For 1 year	1b	A	++
➢ For 2 years	1b	A	-
➢ For 0.5 years	1b	A	+/-

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Further Information

References

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Version 2017.1

Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5 **GR: D** **AGO: ++**

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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Guidelines Breast
Version 2017.1

Adjuvant Treatment with Trastuzumab: Schedules

	Oxford LoE	/ AGO 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

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References

Adjuvant Therapy with Other Targeted Agents

Guidelines Breast
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	Oxford LoE	/ AGO GR	
➢ **Lapatinib**	1b[a]	B	-
➢ **(delayed adjuvant treatment)**	1b	B	-
➢ **Lapatinib + Trastuzumab**	1b[a]	B	-
➢ **Pertuzumab**	5	D	-
➢ **Bevacizumab**	1b	B	--

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Further Information

References

Adjuvant Cytotoxic and Targeted Therapy (2/13)

No further information

No references

Subtype-specific General Systemic Strategies (3/13)

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.
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Adjuvant Chemotherapy without Trastuzumab: Overview (4/13)

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, 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: 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]

Statement: Dose-dense in case of high tumor burden (1a A ++)
Vote result of the AGO recommendation: 100%

1. Moylan EJ, Connell LC, O'Reilly S. Are dose-dense and triplet chemotherapy regimens optimal adjuvant therapy in the majority of women with node-positive early breast cancer? J Clin Oncol. 2014 Feb 20;32(6):605-6.
2. Lemos Duarte I, da Silveira Nogueira Lima JP, Passos Lima CS, Deeke Sasse A. Dose-dense chemotherapy versus conventional chemotherapy for early breast cancer: a systematic review with meta-analysis. Breast. 2012 Jun;21(3):343-9.

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Statement: Low dose maintenance Chemotherapy (1b B -)
Vote result of the AGO recommendation:

1. Colleoni et al., Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early nreast cancer: International Breast Cancer Study Group trial 22-00. J Clin Oncol 2016, 34:3400-8 Epub

Collenoni et al. (5/13)

No further information

No references

Recommended Regimens for Adjuvant Chemotherapy (6/13)

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 A60Cq3w x 4 → P80qw1 x 12 (1b A ++)
Vote result of the AGO recommendation: 100%

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

Statement: Anthracycline/ taxane based regimen
AC → D A60C q3w x 4 → D100 qw3 x 4 (1b A ++)
EC → D E90C q3w x 4 → D100 qw3 x 4 (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 (7/13)

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 nodenegative 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, Cirrincione 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. 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 ≥ 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 (8/13)

Further information and references:

Statement: Capecitabine containing regimen in TNBC (1a B +/-)
Vote result of the AGO recommendation: 100%

1. 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
2. Jiang Y, Yin W, Zhou L, Yan L, Zhou Q, Du Y, Shen Z, Shao Z, Lu J. First efficacy results of capecitabine with anthracycline-and taxane-based adjuvant therapy in high-risk early breast cancer: a meta-analysis. PLoS ONE 2012 7(3): e32474.

Statement: Platinum containing regimen in TNBC (5 D +/-)
Vote result of the AGO recommendation: 100%

No references available.

Statement: 5- Fluorouracile added to EC/AC (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 (9/13)

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, Greatorex 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.
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]
5. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)- negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of

Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 2016 Jul 10;34(20):2416-27. Doi10.1200/JCO2016.67.0182

Statements: >10 mm/> 5-10 mm/ <= 5mm (1a A ++ / 2b B + / 2b B +/-)

1. Denduluri N, Somerfield MR, Eisen A, Holloway JN, Hurria A, King TA, Lyman GH, Partridge AH, Telli ML, Trudeau ME, Wolff AC Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor (Her2)- negative and adjuvant targeted therapy for Her2-positive breast cancers: an American Society of Clinical Oncology Guideline adaptation of the Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol 2016 Jul 10;34(20):2416-27. Doi10.1200/JCO2016.67.0182
2. O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, Costantino JP, Delaloge S, Rastogi P, Zardavas D, Ballman KV, Holmes E, de Azambuja E, Piccart-Gebhart M, Zujewski JA, Gelber RD. Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors ≤ 2 cm: A Meta-Analysis of the Randomized Trastuzumab. J Clin Oncol. 2015 Aug 20;33(24):2600-8. doi: 10.1200/JCO.2015.60.8620. Epub 2015 Jun 22.

Adjuvant Treatment with Trastuzumab II (10/13)

Further information and references:

Statement: Start of treatment simultaneously with taxanes (1 A ++)
Vote result of the AGO recommendation: 100%

1. 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.
2. 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
3. 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.
4. 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.
5. 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

6. 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.
7. 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 – Cardiac Monitoring for CHF (11/13)

Further information and references:

Statement: Cardiac Monitoring (5 D ++)
Vote result of the AGO recommendation: 100%

1. 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.
2. 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.
3. Curr Oncol. 2008 Feb;15(1):24-35.

Adjuvant Treatment with Trastuzumab: Schedules (12/13)

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

Statement: P q1w12 without A in pT < 3 cm pN0 (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, Mrsic-Krmpotic Z, Jagiello-Gruszfeld 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 7.

Statement: with taxanes dose-dense (2b B+)
Vote result of the AGO recommendation: 100%

See references slide 7.

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 (13/13)

Further information and references:

Statement: with Lapatinib (1b[a] B -)
Delayed adjvuvant 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, Ejlertsen B, Kaufmann M, Boyle F, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Chavarri-Guerra Y, Aktan G, Rappold E, Williams LS, Finkelstein DM; TEACH investigators. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013 Jan;14(1):88-96.
3. 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

Statement: Neratinib after adjuvant trastuzumab (1b[a] B +/-)
Vote result of the AGO recommendation:

1. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, Robert NJ, Silovski T, Gokmen E, von Minckwitz G, Ejlertsen B, Chia SK, Mansi J, Barrios CH, Gnant M, Buyse M, Gore I, Smith J 2nd, Harker G, Masuda N, Petrakova K, Zotano AG, Iannotti N, Rodriguez G, Tassone P, Wong A, Bryce R, Ye Y, Yao B, Martin M; ExteNET Study Group..

Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2016 Mar;17(3):367-77. doi: 10.1016/S1470-2045(15)00551-3. PMID: 26874901

Guidelines Breast
Version 2017.1

Neoadjuvant
(Primary) Systemic Therapy

START

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Neoadjuvant Systemic Therapy

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References

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Subtype-specific General Systemic Strategies

	AGO
If chemotherapy is indicated due to tumor biology, consider systemic treatment before surgery (neoadjuvant)	++
HR+/HER2- and "low risk":	
➢ Endocrine therapy without chemotherapy	++
HR+/HER2- and "high risk"	
➢ Conventionally dosed AT-based chemotherapy	++
➢ Dose dense & escalated in case of high tumor burden	+
➢ Followed by endocrine therapy	++
HER2+	
➢ Trastuzumab (plus Pertuzumab neoadjuvant) 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	+

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References

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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

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References

Neoadjuvant Systemic Chemotherapy Indications

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	Oxford / AGO LoE / GR		
➢ Inflammatory breast cancer	2b	B	++
➢ Inoperable breast cancer	1c	A	++
➢ Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation	1b	B	+
➢ If similar postoperative adjuvant chemotherapy is indicated	1b	A	+

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Neoadjuvant Systemic Chemotherapy Response Prediction I

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

Factor	LoE_{2009}	CTS	GR	AGO
➢Multigene signatures	III	C	B	+/-
➢Ki-67	I	B	A	+
➢Tumor infiltrating lymphocytes*	I	B	B	+
➢*PIK3CA* mutation	I	B	B	+/-
➢*gBRCA in TNBC*	II	B	B	+

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

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Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

	Oxford / AGO LoE	GR	
➢ Standard protocols used in the adjuvant setting with a duration of at least 18 weeks	1a	A	++
➢ AC or EC → D q3w or P q1w	2b	A	++
➢ DAC	2b	B	++
➢ Taxane followed by anthracycline	1a	A	+
➢ Dose-dense regimen (e.g. E -P-CMF, E-P-C)	1b	B	+*
➢ Platinum in TNBC (irrespective of BRCA status)	2b	B	+
➢ Nab-Paclitaxel weekly instead of Paclitaxel weekly	1b	B	+/-

*Study participation recommended

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Potential Carboplatin Containing Regimens in the Neoadjuvant Setting

Author	Study	Regimen	pCR rate	3-yr EFS rates
Sikov WM, et al. JCO 2015 SABCS 2015	CALGB 40603 Phase II	Paclitaxel 80mg/m² 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/m² qw x18 + Paclitaxel 80mg/m² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15 mg/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/m² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4	TNBC ± Cb: 61% vs. 26%	

Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response

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	Oxford / AGO LoE / GR		
➢ Breast ultrasound	2b	B	++
➢ Palpation	2b	B	++
➢ Mammography	2b	B	++
➢ MRI	2b	B	+
➢ PET(-CT)*	2b	B	+/-
➢ Clip tumor region	5	D	++
➢ Clip positive lymph node	3	C	+/-

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* Study participation recommended

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Neoadjuvant Targeted Therapy in HER2 Positive Tumors

	Oxford / AGO LoE	GR	
➢ Trastuzumab in combination with chemotherapy	1b	A	++
➢ Pertuzumab + Trastuzumab in combination with chemotherapy	2b	B	++
➢ Lapatinib in combination with chemotherapy	1a	B	-
➢ Lapatinib + Trastuzumab in combination with chemotherapy	1a	B	+/-
➢ Two anti-HER2 agents without chemotherapy	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** — **1b A ++**
- **In case of response after 2 cycles of DAC in HR positive breast cancer consider 8 instead of 6 cycles of DAC** — **2b C +**

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Neoadjuvant Systemic Therapy
Procedures in Case of No Early Response

	Oxford / AGO LoE / GR		
In case of no change:			
➢ Completion of NST, followed by surgery	2b	C	++
➢ Continuation of NST with non cross-resistant regimen	2b	B	+
➢ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
➢ DAC x 2 → NX x 4	1b	B	+
In case of progressive disease:			
➢ Stop of NST and surgery or radiotherapy	4	D	++*
➢ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-*

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* Study participation recommended

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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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				Oxford / AGO LoE / GR		
SLNB before or after NACT in cN0						
SLNB before NACT **SLNB after NACT**				**2b** **2b**	**B** **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+	**pN+ (CNB/FNA)**	**ycN0** **ycN+**		**SLNB alone*** **ALND** **ALND**	**2b** **2b** **2b**	**B** **B** **B**	**+/-** **+** **++**

Neoadjuvant Systemic Therapy
Indications for Mastectomy

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	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

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	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**	1a	A	++
➢ **Complete trastuzumab treatment for 1 year in HER2-positive disease**	2b	B	++
➢ **Complete pertuzumab treatment for 1 year in HER2-positive disease**	3	C	-
➢ **If insufficient response in case of non-pCR (invasive residual tumor in the breast and / or axillary nodes) after adequate NACT (antracyclines, taxanes, 18 weeks)**			
➢ **Capecitabine adjuvant in TNBC**	2b[a]	B	+/-
➢ **Further chemotherapy**	3	C	-
➢ **Experimental therapies in clinical trials**	5	D	+

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Neoadjuvant Endocrine Therapy
in Patients with Endocrine-responsive Breast Cancer

	Oxford / AGO LoE	GR	
Postmenopausal patients:			
Who are inoperable and can / will not receive chemotherapy	2a	B	+
Optimizes the option for breast conserving therapy	1b	A	+
Aromatase inhibitors (for > 3 months)	1a[a]	B	+
Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
Premenopausal patients			
Who are inoperable and can / will not receive chemotherapy	5	C	+
Tamoxifen	2b	C	+
Aromatase inhibitors + LHRH	1b	C	+/-
Concurrent chemo-endocrine therapy	1b	A	-
Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status	1b	B	+

Optimal duration of neoadjuvant endocrine therapy is unknown

No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

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Further Information

References

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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. Outcome after neoadjuvant chemotherapy in young breast cancer patients: a pooled analysis of individual patient data from eight prospectively randomized controlled trials.Breast Cancer Res Treat. 2015;152(2):377-87.

cT1 / cT2 tumors o. N0 o. G3
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

Negative ER and PgR status
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

Triple negative breast cancer (TNBC)
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

Positive HER2 status
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

Non-lobular tumor type
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

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
3. Stover DG, Coloff JL, Barry WT, Brugge JS, Winer EP, Selfors LM.The Role of Proliferation in Determining Response to Neoadjuvant Chemotherapy in Breast Cancer: A Gene Expression-Based Meta-Analysis. Clin Cancer Res. 2016 Dec 15;22(24):6039-6050
4. Ali HR, Chlon L, Pharoah PD, Markowetz F, Caldas C Patterns of Immune Infiltration in Breast Cancer and Their Clinical Implications: A Gene-Expression-Based Retrospective Study. PLoS Med. 2016 Dec 13;13(12):e1002194. doi: 10.1371/journal.pmed.1002194

Ki-67
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Du Y, et al. The role of topoisomerase IIα 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

4. Ellis MJ, et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance). J Clin Oncol. 2017 Jan 3:JCO2016694406. [Epub ahead of print]
5. Diaz-Botero S, et al. Different Prognostic Implications of Residual Disease After Neoadjuvant Treatment: Impact of Ki 67 and Site of Response. Ann Surg Oncol. 2016 Nov;23(12):3831-3837

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
5. Ingold Heppner B, et al. Tumor-Infiltrating Lymphocytes: A Predictive and Prognostic Biomarker in Neoadjuvant-Treated HER2-Positive Breast Cancer. Clin Cancer Res. 2016 Dec 1;22(23):5747-5754.

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

3. Loibl S, Integrated Analysis of PTEN and p4EBP1 Protein Expression as Predictors for pCR in HER2-Positive Breast Cancer. Clin Cancer Res. 2016 1;22(11):2675-83.
4. Loibl S, PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol. 2016;27(8):1519-25.

gBRCA mutation

Abstimmungsergebnis der AGO-Empfehlungen:

1. Spugnesi L, et al. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. Genes Chromosomes Cancer. 2016 Dec;55(12):915-924.

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, 2×2 factorial randomised phase 3 trial. Lancet Oncol 2014: 15; 201

Dose-dense regimen (e.g. E -P-CMF, E-P-C)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

Platinum in TNBC (irrespective of BRCA status)
Abstimmungsergebnis der AGO-Empfehlungen: XXX

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

<u>Nab-Paclitaxel weekly instead of Paclitaxel weekly</u>
Abstimmungsergebnis der AGO-Empfehlungen

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
2. Gianni L, et al. ETNA ASCO 2016
3. Futamura M, et al.Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: a multicenter phase II trial.Breast Cancer. 2017 Jan 3. doi:
4. Zong Y, Wu J, Shen K Nanoparticle albumin-bound paclitaxel as neoadjuvant chemotherapy of breast cancer: a systematic review and meta-analysis. Oncotarget. 2017 Jan 3.

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

Further information and references:

1. Rauch GM, et al. Multimodality Imaging for Evaluating Response to Neoadjuvant Chemotherapy in Breast Cancer. AJR Am J Roentgenol. 2016 Nov 3:1-10

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
4. Schwentner L,et al. Using ultrasound and palpation for predicting axillary lymph node status following neoadjuvant chemotherapy - Results from the multi-center SENTINA trial. Breast. 2017 Feb;31:202-207.

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
4. Bolan PJ, et al. MR spectroscopy of breast cancer for assessing early treatment response: Results from the ACRIN 6657 MRS trial. J Magn Reson Imaging. 2016 Dec 16. doi: 10.1002/jmri.25560. [Epub ahead of print]

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
3. Groheux D,et al. ¹⁸FDG-PET/CT for predicting the outcome in ER+/HER2- breast cancer patients: comparison of clinicopathological parameters and PET image-derived indices including tumor texture analysis. Breast Cancer Res. 2017 Jan 5;19(1):3

Clip tumour region

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

1. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, Bedrosian I, Hobbs BP, DeSnyder SM, Hwang RF, Adrada BE, Shaitelman SF, Chavez-MacGregor M, Smith BD, Candelaria RP, Babiera GV, Dogan BE, Santiago L, Hunt KK, Kuerer HM.Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. J Clin Oncol. 2016;34(10):1072-8.

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
10. Jackisch C, Hegg R, Stroyakovskiy D, Ahn JS, Melichar B, Chen SC, Kim SB, Lichinitser M, Starosławska E, Kunz G, Falcon S, Chen ST, Crepelle-Fléchais A, Heinzmann D, Shing M, Pivot X.HannahHannaH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. Eur J Cancer. 2016 Jul;62:62-

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)
5. Loibl S, et al. Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. Ann Oncol. 2016 Nov 9. pii: mdw610. [Epub ahead of print]

Two anti-HER2 agents without chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

Anti-HER2 agent in combination with endocrine treatment
Abstimmungsergebnis der AGO-Empfehlungen: 3+, 16+/-, 6-

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

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

Further information and references:

Bevacizumab in combination with chemotherapy in hormone receptor positive
Abstimmungsergebnis der AGO-Empfehlungen: 13+/-, 17-

1. Von Minckwitz G, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. N Engl J Med 2012: 366; 299
2. Bear HD, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med 2012: 366; 310
3. Von Minckwitz G, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44-GeparQuinto)†. Ann Oncol 2014: 25; 2363
4. Smith JW, 2nd, Buyse ME, Rastogi P, Geyer CE, Jr., Jacobs SA, Patocskai EJ, et al. Epirubicin With Cyclophosphamide Followed by Docetaxel With Trastuzumab and Bevacizumab as Neoadjuvant Therapy for HER2-Positive Locally Advanced Breast Cancer or as Adjuvant Therapy for HER2-Positive Pathologic Stage III Breast Cancer: A Phase II Trial of the NSABP Foundation Research Group, FB-5. Clin Breast Cancer 2016.

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
6. Ma X, et al. Bevacizumab Addition in Neoadjuvant Treatment Increases the Pathological Complete Response Rates in Patients with HER-2 Negative Breast Cancer Especially Triple Negative Breast Cancer: A Meta-Analysis. PLoS
7. Nahleh ZA, Barlow WE, Hayes DF, Schott AF, Gralow JR, Sikov WM, et al. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rates in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat 2016;158(3):485-95.One 2016;11(8):e0160148.
8. Bertucci F, Fekih M, Autret A, Petit T, Dalenc F, Levy C, et al. Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. Lancet Oncol 2016;17(5):600-11.

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

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
3. Colleoni M, Gray KP, Gelber S, Lang I, Thurlimann B, Gianni L, et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.

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
4. El Hage Chehade H, Headon H, El Tokhy O, Heeney J, Kasem A, Mokbel K.Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016 Nov;212(5):969-981.

5. Mamtani A, et al. How Often Does Neoadjuvant Chemotherapy Avoid Axillary Dissection in Patients With Histologically Confirmed Nodal Metastases? Results of a Prospective Study. Ann Surg Oncol. 2016 Oct;23(11):3467-74.

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
2. Brzezinska M, Williams LJ, Thomas J, Michael Dixon J. Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. Breast Cancer Res Treat 2016;160(3):387-91.

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

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
2. Omarini C, Guaitoli G, Noventa S, Andreotti A, Gambini A, Palma E, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol 2016.
3. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. Ann Surg Oncol 2016;23(5):1515-21.

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 (antracyclines, taxanes, 18 weeks)

1. von Minckwitz G, Rezai M, Tesch H, Huober J, Gerber B, Zahm DM, Hilfrich J, Costa SD, Dubsky P, Blohmer JU, Denkert C, Hanusch C, Jackisch C, Kümmel S, Fasching PA, Schneeweiss A, Paepke S, Untch M, Burchardi N, Mehta K, Loibl S; German Breast Group and Austrian Breast and Colon Cancer Study Group Investigators.Zoledronate for patients with invasive residual disease after anthracyclines-taxane-based chemotherapy for early breast cancer - The Phase III NeoAdjuvant Trial Add-oN (NaTaN) study (GBG 36/ABCSG 29). Eur J Cancer. 2016 ;64:12-21.

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

1. Colleoni M, Gray KP, Gelber S, Lang I, Thurlimann B, Gianni L, et al. Low-Dose Oral Cyclophosphamide and Methotrexate Maintenance for Hormone Receptor-Negative Early Breast Cancer: International Breast Cancer Study Group Trial 22-00. J Clin Oncol 2016;34(28):3400-8.
2. Tanaka S, et al. A Phase II Study of Adjuvant Chemotherapy of Tegafur-Uracil for Patients with Breast Cancer with HER2-negative Pathologic Residual Invasive Disease After Neoadjuvant Chemotherapy. Anticancer Res. 2016 Dec;36(12):6505-6509

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
5. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016;2(11):1477-86.

AI and fulvestrant

1. Lerebours F, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer. 2016 Oct;122(19):3032-40.

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; 339Von 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
2. 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
3. Rimawi M, al. e. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG oncology/NSABP B-52. San Antonio Breast Cancer Symposium 2016:Abstract S3-06.
4. Spring LM, et al. Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016 Nov 1;2(11):1477-1486.

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

Guidelines Breast
Version 2017.1

Adjuvant Radiotherapy

START

Adjuvant Radiotherapy (RT)

- **Versions 2002–2015:**
  Blohmer / Budach / Friedrichs / Göhring / Janni / Kühn / Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

- **Version 2016:**
  Thomssen / Budach / Wenz

- **Version 2017:**
  Blohmer / Budach / Scharl / Wenz

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Further Information

References

Preliminary Note

- **The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between experts of the AGO and DEGRO**
- **For technical details of radiotherapy we recommend to refer to the corresponding updated DEGRO practical guidelines 2014-2016**
- **If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue color**

Guidelines Breast
Version 2017.1

Guidelines and Opinions

St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:
Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. **Hypofractioned 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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Further Information

References

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

Guidelines Breast
Version 2017.1

	Oxford LoE	/ AGO GR	
➢ Radiotherapy of the affected breast	1a	A	++
➢ Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks	1a	A	++
➢ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)	1a	B	+
➢ In case of life expectancy <10 years and pT1, pN0, R0, ER/PR positive, HER2 negative, endocrine therapy (all criteria) radiotherapy can be omitted after individual counseling accepting an increased risk of in breast recurrence	1a	B	+

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Further Information

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Additional Information with Regard to Effects of Breast Radiotherapy (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 advised about the following :**
  - **In older patients with pT1-2 (=<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.**

BCS >=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 (Δ=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.)

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

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

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ **Boost-RT (improves local control, no survival benefit)**			
➢ Premenopausal	1b	B	++
➢ Postmenopausal, if >T1, G3, HER2-positive, triple negative, EIC (at least 1 factor)	2b	B	+
➢ **Intraoperative irradiation (intraop. APBI)**			
➢ As boost-irradiation followed by WBI	2a	B	+
➢ As sole radiotherapy modality (IORT 50 kV, IOERT)**			
➢ >50 years**	1a	A	+/-*
➢ >70 years**	1a	A	+
➢ **Postoperative partial breast irradiation as sole radiotherapy modality (APBI)**			
➢ Interstitial brachytherapy	1b	B	+/-*
➢ >70 years**	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

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Further Information

References

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EORTC 22881-10882: Boost vs no Boost
(Endpoint: Ipsilateral Breast Recurrence)

Guidelines Breast
Version 2017.1

@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

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Further Information

References

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

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

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Further Information

References

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ > 3 tumor infiltrated lymph nodes (Lnn.)	1a	A	++
➢ 1–3 tumor infiltrated Lnn. (high risk)	1a	A	+
➢ 1–3 tumor infiltrated Lnn. (low risk*)	5	D	+/-
➢ T3 / T4	1a	A	++
➢ pT3 pN0 R0 (and no additional risk factors)	2b	B	+/-
➢ If R0 is impossible to reach (for invasive tumor)	1a	A	++
➢ In young pts with high risk features	2b	B	++
➢ After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+ (CNB/FNA), cT3/4a-d)	2a	B	+
➢ Omission of RT if ypT0 ypN0 after NACT**	2b	B	+/-
The indications for PMRT and regional RT are independent of adjuvant systemic treatment	1a	A	

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Further Information

References

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*For definition of risk, go to Further information

**Study participation recommended

Radiotherapy of the Chest Wall After Mastectomy (PMRT) in Case of 1-3 Axillary Lymph Node Metastases

Guidelines Breast
Version 2017.1

PMRT can be omitted	PMRT to be discussed	PMRT recommended
LoE 3b B AGO +	**LoE 3b B AGO +/-**	**LoE 3b B AGO +**
ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)	Applies for patients, who don‘t fulfill the mentioned criteria for high or low risk	≥45 y. AND >25% pos. ax. Lnn in case of axillary dissection OR <45 y. AND (ER neg. OR>25% pos. ax. Lnn in case of axillary dissection OR medial tumor location)
Kyndi et al. 2013		Truong et al. 2005
		<40 y. OR HER2 pos. OR lymphovascular invasion
		Shen H et al. 2015
		G3 OR lymphovascular invasion OR triple negative
		Different publications

Comment: In case of an indication for radiotherapy of regional lymph nodes, radiotherapy of the chest wall should also be administered

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Further Information

References

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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Further Information

References

Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
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 not met	1b	B	++*
➢ If mastectomy: PMRT and ACOSOG Z0011-criteria not met, or PMRT not planned	1b	B	++
>=3 pos. SLN:			
➢ Axillary dissection	1b	B	++
➢ Radiotherapy of the axilla	1b	B	+

*Study participation recommended

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Further Information

References

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* *tumor central or medial and (G2-3 or ER/PgR-negative) *tumor lateral and premenopausal and (G2-3 or ER/PgR-negative)	2a	B	+
➢ 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) AGO[1]	2b	B	+/-
➢ After NACT/NAT if cN+ (CNB/FNA) (ind. as for PMRT) DEGRO[1]	2b	A	+

[1] Different interpretation of published data by AGO and DEGRO

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Further Information

References

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

Internal mammaria lymph node region (IMN)	Oxford LoE	/AGO GR	
➢ pN0 high risk*** with central or medial tumor	1b	B	+/-
***premenopausal and G2-3 and ER/PgR-negative			
➢ 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)			
➢ pN2a high risk**	2a	B	+
**G2-3 or ER/PgR-negative			
➢ 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) AGO[1]	2b	B	+/-
➢ After NACT/NAT if cN+ (CNB/FNA) (ind. acc. PMRT) DEGRO[1]	2b	A	+

[1] Different interpretation of published data by AGO and DEGRO

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Further Information

References

Fractionation of Radiotherapy in Case of Radiotherapy of the Regional Lymph Nodes

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE /GR	
➢ Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)	1a A	++
➢ Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)	2b B	+/-

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

Guidelines Breast
Version 2017.1

(median follow-up 10.9 yrs)

Adjuvant treatment	**n***	**Hazard ratio (95%CI)**
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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Further Information

References

Concomitant Use of Systemic Therapy with Radiotherapy

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR
➢ **Trastuzumab* concurrent with radiotherapy**	**2b B +**
➢ **Tamoxifen concurrent with radiotherapy**	**2b B +**
➢ **AI (letrozole, anastrozole) concurrent with radiotherapy**	**2b B +**

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

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Further Information

References

Interaction between Smoking and Risk of Irradiation-induced Side Effects

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR	
➢ Enhanced risk of lung cancer secondary to breast cancer radiotherapy in smokers	1a	A
➢ Inform patients about the risk		++
➢ Recommend to stop smoking		++

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Further Information

References

Adjuvant Radiotherapy (2/20)

Further information:

Search Strategy
Search Terms: Radiotherapy Breast Cancer
Source: Pubmed 1/2010 – 1/2017

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 (3/20)

Further information:

AGO – Arbeitsgemeinschaft für Gynäkolgische 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.

Guidelines and Opinions (4/20)

No further information

References:

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Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Whole Breast Irradiation (5/20)

Further information:

Basically, data on hypofractionation in PMRT and BCT are valid for all subgroups and age groups. Hypofractionation is the standard radiation therapy after breast conserving surgery. 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, hypofractioned 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 ½). (Harris JR SABCS 2015)

Update 2017.
Hypofractionated radiotherapy is now the standard radiotherapy after breast conserving surgery because of better outcome and lower toxicity compared with conventional fractionated radiotherapy (50 Gy over 6 week with or without boost). Conventional fractionated radiotherapy is also possible. In older patients with low-risk breast cancer radiotherapy after breast conserving therapy can be avoided. Informed consent with patient is necessary. Patients report more higher grade radiation associated toxicity than physicians.

Radiotherapy in Elderly Patient Life Expectancy less than 10 Years:

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. Haviland JS[1], Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
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3. Haffty BG[1], Buchholz TA. Hypofractionated breast radiation: preferred standard of care? Lancet Oncol. 2013 Oct;14(11):1032-4.
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Additional Information with Regard to Effects of Breast Radiotherapy (BCT) (6/20)

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 trails: “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:

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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.
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4. 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 (7/20)

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 (8/20)

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

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Boost-RT in premenopausal p. (LoE 1b A AGO++)

Boost-RT in postmenopausal p. (LoE 2b B AGO+)

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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 ISIORT pooled analysis. Fastner G, Sedlmayer F, Merz F, Deutschmann H, Reitsamer R, Menzel C, Stierle C, Farmini A, Fischer T, Ciabattoni A, Mirri A, Hager E, Reinartz G, Lemanski C, Orecchia R, Valentini V. Radiother Oncol. 2013 Aug;108(2):279-86.
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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 1a A AGO+/-)

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<u>>70 yrs LoE 1a A AGO+</u>

1. Abbott AM[1], Dossett LA[1], Loftus L[1], Sun W[1], Fulp W[2], Sokol GH[3], Laronga C[4]. Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. Am J Surg. 2015 Oct;210(4):624-8.
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Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)
Interstitial brachytherapy (LoE 1b B AGO+/-)

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

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Intracavity balloon technique (LoE 1b B AGO-)

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IMRT (LoE 1b B AGO-*)

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EORTC 22881-10882: Boost vs no Boost (9-10/20)

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.

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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.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall (11-12/20)**

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.
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5. Jagsi R. Postmastectomy radiation therapy: an overview for the practicing surgeon. ISRN Surg. 2013 Sep 11;2013:212979.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.) (LoE1a A AGO++):

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

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

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med. 1997 Oct 2;337(14):949-55.
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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]

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

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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6. NCCN Guidelines for Treatment of Cancer by Site "http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf" download 2016

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

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

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

1. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014 Jun 21;383(9935):2127-35.
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1. Garg AK, Oh JL, Oswald MJ, et al. Eff ect 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.
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Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. after neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d) (LoE 2a A AGO+):

1. Wright JL, Takita C, Reis IM, Zhao W, Saigal K, Wolfson A, Markoe A, Moller M, Hurley J. Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. Cancer. 2013 Jan 1;119(1):16-25.
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.

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4. Rusthoven CG[1], Rabinovitch RA[1], Jones BL[1], Koshy M[2], Amini A[1], Yeh N[1], Jackson MW[1], Fisher CM[1]. 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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Radiotherapy of the Axilla (13/20)

Fu*rther information*
In 2017 a new Cochrane analysis regarding axillary treatment was published and pointed out again that in clinically node negative axilla all axillary interventions are mainly diagnostic and not therapeutic.

References:

new:
Bromham N, Schmidt-Hansen M, Astin M, Hasler E, Reed MW. Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017 Jan 4;1:CD004561. doi: 10.1002/14651858.CD004561.pub3. [Epub ahead of print]

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 fi ndings 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.
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4. Lyman GH, Giuliano AE, Somerfi eld 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 (14/20)

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

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

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

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

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

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

EXPERT OPINION, extrapolated from:

1. Giuliano AE, Hunt KK, Ballmann KV, Bartsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M. Axillary dissection vs no axillary dissection in women with breast invasive cancer and sentinel node metastasis. A randomised clinical trial. JAMA 2011;305(6):569-5753.
2. Galimberti V1, Cole BF, Zurrida 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.
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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG) (15/20)

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 infra-clavicular 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.

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

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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.

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

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

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN) - Slide 16/20

No further information

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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.
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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+

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Fractionation of Radiotherapy in Case of Radiotherapy of the Regional Lymph Nodes (17/20)

No further information

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Multivariate Analysis of Overall Surival: Effect of Radiotherapy of the Internal mammaria Lymph Nodes (18/20)

No further information

No references

Concomitant Use of Systemic Therapy with Radiotherapy (19/20)

No further information

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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).
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3. Chung C, Stuart D, Keves M. Radiation recall reaction induced by adjuvant trastuzumab (Herceptin). Case Report Med 2009;2009:307894.
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Tamoxifen concurrent with radiotherapy (LoE 2b B AGO +)

1. Chargari C[1], 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.
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AI (letrozole, anastrozole) concurrent with radiotherapy (LoE 2b B AGO +)

1. Chargari C[1], Toillon RA, Macdermed D, Castadot P, Magné N. Concurrent hormone and radiation therapy in patients with breast cancer: what is the rationale? Lancet Oncol. 2009 Jan;10(1):53-60.
2. Belkacémi Y, Fourquet A, Cutuli B, et al. Radiotherapy for invasive breast cancer: Guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 2011;79:91-102
3. Valakh V, Trombetta MG, Werts ED, et al. Influence of concurrent anastrozole on acute and late side effects of whole breast radiotherapy. Am J Clin Oncol 2011;34:245-8
4. Ishitobi M, Nakahara S, Komoike Y, et al. Risk of ipsilateral breast tumor recurrence in patients treated with tamoxifen or anastrozole following breast-conserving surgery with or without radiotherapy. Anticancer Res 2011;31:367-371.

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Other compounds (bevacizumab)

1. Late toxicities and outcomes after one year of adjuvant radiotherapy combined with concurrent bevacizumab in patients with triple negative non-metastatic breast cancer. Pernin V, Belin L, Cottu P, Bontemps P, Lemanski C, De La Lande B, Baumann P, Missohou F, Levy C, Peignaux K, Reynaud-Bougnoux A, Denis F, Gobillion A, Bollet M, Dendale R, Campana F, Fourquet A, Kirova YM. Br J Radiol. 2015 Feb 3:20140800.

Interaction between Smoking and Risk of Irradiation-induced Side effects (20/20)

No further information

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Further Information

References

Toxicity Assessment

Acute Toxicity

According to WHO[1] or NCI-CTC[2]

Grade	Information required
0 none	organs involved
1 mild	type of toxicity
2 moderate	time interval after treatment
3 severe	effect on general health status
4 life threatening	treatment required
5 death	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 v4.03, (2010) http://evs.nci.nih.gov/ftp1/CTCAE/About.html
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Acute Toxicity (NCI CTCAE vs 4.03, 2010)

- **Grade 1**
  Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**
  Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- **Grade 3**
  Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.**
- **Grade 4**
  Life-threatening consequences; urgent intervention indicated.
- **Grade 5**
  Death related to AE.

Activities of Daily Living (ADL)

***Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.**

****Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.**

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Cytotoxic Anti-Cancer Drugs
Acute Toxicity I

	Haematol. Toxicity	Nausea/ Vomit.	Alopecia	Mucositis/ Stomatits	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	++	+	+				

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Cytotoxic Anti-Cancer Drugs
Acute Toxicity II

	Allergy	Bladder	Neuro-toxicity	Cutane Tox	Diarrhea	
Cyclophosphamide	+	+	+	+		
Methotrexate	+		+	++		
5-Fluorouracil				+	+	
Carboplatin						
Cisplatin			+++			
Capecitabine				++	++	
Gemcitabine						**Flue-like Synd., Edema**
Epi-/Doxorubicin	+					**Paravasate, Dexraxozane**
Liposomal Doxo.	+			+		
Pegliposomal Doxo.	+			+++		
Mitoxantrone						
Paclitaxel	+++		++		+	**Myalgia**
nab-Paclitaxel	+		++		+	**Myalgia**
Docetaxel	++		+	++	+	**Myalgia, Fluid retention, nails!**
Vinorelbine			++			**Thrombophlebitis, Obstipation**
Eribulin				++		

Peripheral Neuropathy

- **Incidence grade 1-2 after taxane therapy 20-50 %**
- **Incidence grade 3-4 after taxane therapy 6-20 %**
- **Risk factors: Type of chemotherapy, dose, BMI, no physical activity**

- **Individual risk factors:**
  - **Diabetes mellitus**
  - **Nutritionally toxic substances (e.g. alcohol)**
  - **Renal insufficiency**
  - **Hypothyroidism**
  - **Collagenosis / Vasculitis**
  - **Vitamine deficiency**
  - **HIV-Infection**
  - **CMT-Gene Mutation**

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References

S3 Guideline November 2016

Chemotherapy Induced Peripheral Neuropathy

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	Oxford / AGO LOE / GR		
Prophylaxis			
➢ **Non drug**			
➢ **Functional training**	**2c**	**C**	**+**
➢ **Peripheral compressions therapy**	**2b**	**B**	**+**
➢ **By drugs**	**1b**	**B**	**-**

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Long-Term Toxicity
Cardiotoxicity

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	Oxford / AGO LoE	GR	
➢ Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)	2b	B	
➢ Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity	1b	B	
➢ Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:	2b	B	
➢ Elderly patients			
➢ Obesity			
➢ Hypertension			
➢ Hypercholesterolemia			
➢ Pre-existing cardiac diseases (incl. borderline LVEF)			
➢ Diabetes mellitus			
➢ Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)	3b	C	+

Feasibility of Treatment Combinations Considering Toxicities

	Oxford / AGO LoE	GR	
Regarding cardiac toxicity			
➢ Trastuzumab simultaneous to radiotherapy	2b	B	+
➢ Trastuzumab simultaneous to epirubicin	2b	B	+/-
➢ Trastuzumab simultaneous to doxorubicin	2b	B	-
➢ Anthracycline simultaneous to radiotherapy	2c	C	-
Regarding lung and breast fibrosis			
➢ Tamoxifen simultaneous to radiotherapy	3	C	+/-
➢ Chemotherapy simultaneous to radiotherapy	1b	B	-

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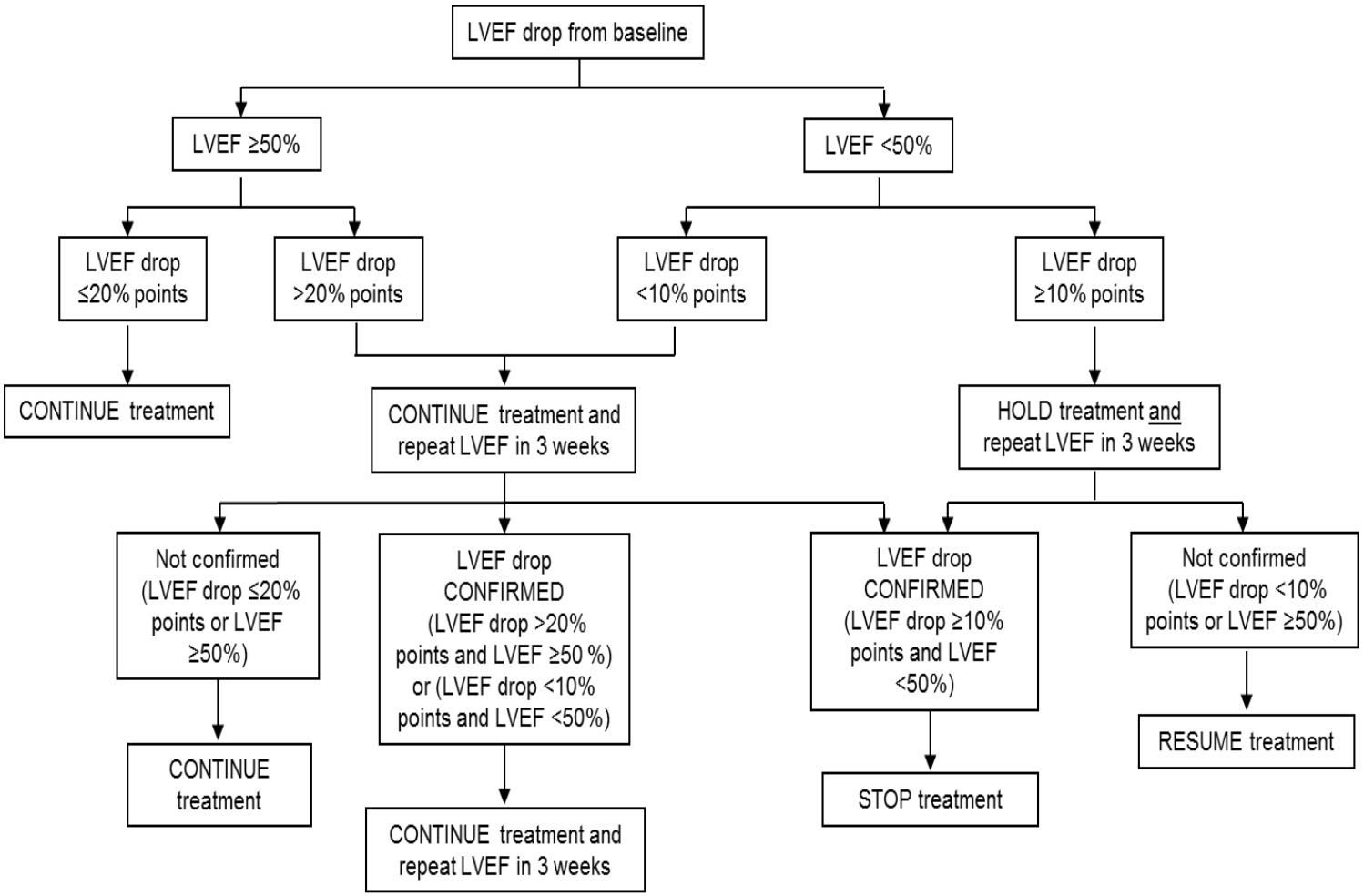
References

Side Effects of Trastuzumab/Pertuzumab Algorithm in Case of Cardiac Toxicity



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Secondary Malignancies I

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	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-inihibitors 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

Secondary Malignancies II (after Radiotherapy)

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	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**	**2b**
➢ **Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15 / 10.000) 5–10 years after treatment**	**1a**
➢ **Enhanced risk especially among ever smokers**	**2b**
No difference of secondary malignancy between PBI und WBI	**2c**

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References

Chemotherapy Related Amenorrhea (CRA)

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	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)

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References

(Therapy Related) Fatigue

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
➢ Fatigue frequently present in breast cancer patients (30–60%)	2a	B	
➢ Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue	1a	A	++
➢ Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue	1a	A	++
➢ Physical exercise can improve fatigue	1b	D	+
➢ Diet, Yoga can improve fatigue	2b	B	+
➢ Methylphenidate can improve fatigue	1a	D	+

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References

(Therapy Associated) Sleeping disturbance

Guidelines Breast
Version 2017.1

	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

Guidelines Breast
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	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	
➢ Antidepressents have shown to improve depression in breast cancer patients	1b	A	
➢ Regular exercise participation can prevent depression among breast cancer survivors	2b	B	+

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(Therapy Associated) Cognitive Impairment

	Oxford / AGO LoE / GR	
➢ Therapy-related cognitive deficits (chemobrain frequently described (16–75%))	2a	B
➢ Cognitive-behavioral therapy is beneficial for cognitive function	2b	B
➢ Methylphenidate might improve cognitive function in patients with cancer	3a	C

Side-effects and Toxicity of Endocrine Agents

	Visual Disturbances	Osteoporosis	Cerebro-Vascular Events *	Fracture	Cardiac risk	Cognitive functions
SERMs	(+)		+			+
AI 3rd Gen*		+		+	+	(+)
SERD (Fulvestrant)		+		+		
GnRHa		+		+		

	Arthralgia Myalgia	Flush	Dysfunctional Bleeding*	Endometrial Changes	Deep Venous Thrombosis	Lipid Profile Impaired
SERMs	(+)	+	+	+	(+)	
	(+)	+	+	+		
AIs	+	(+)				(+)
SERD (Fulvestrant)						
Goserelin	(+)	+				

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Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

Guidelines Breast
Version 2017.1

	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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References

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**

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References

Frequent Side Effects of Bone Modifying Agents (BMA)

Guidelines Breast
Version 2017.1

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.						
q4w or q12w	+	+	0	0	+	
Pamidronate 90 mg i.v.	+	+	0	0	+	
Zoledronate 4 mg i.v. q6m	+	0	0	0	0	
Denosumab 120 mg sc q4w	0	0	0	+	+	Hypo-calcemia

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Key-Toxicities – Antibodies/Antibody-drug-conjugates

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	Oxford / AGO LoE / GR
Trastuzumab	
➢ Cardiotoxicity in the adjuvant setting (0,8–4,0%)	1b A
➢ Troponin I might identify patients who are at risk for cardiotoxicity	2b B
Bevacizumab	
➢ Hypertonus, proteinuria, bleeding, left ventricular dysfunction,	1a A
Pertuzumab	
➢ Skin rash, diarrhea, mucositis	2b B
T-DM1	
➢ Thrombocytopenia, hepatotoxicity pyrexia, headache, pneumonitis	2b B

Small Molecules

	Oxford / AGO LoE	GR
Lapatinib		
➢ Diarrhea, skin rash, fatigue	1b	A
Everolimus		
➢ Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, thrombocytopenia	2b	B
PARP-inhibitors (olaparib)		
➢ Fatigue, myelosuppression	3	C
CDK4/6 inhibitors (palbociclip, LEE011)		
➢ Myelosuppression, neutropenia	3	C

Immun-Checkpoint Inhibitors

Guidelines Breast
Version 2017.1

- **Therapeutic options (Antibodies)**
  - **PD1 /PD-L1**
    - **Nivolumab**
    - **Pembrolizumab**
    - **Atezolizumab**
  - **CTLA-4**
    - **Ipilimumab**

Immune-Checkpoint Inhibitors

- **Side effects ≥ Grade 3**
  - **Diarrhea**
  - **Fatigue**
  - **Colitis**
  - **Hypophysitis**
  - **Hepatitis**
  - **Skin changes**
  - **Thyreoiditis**

Guidelines Breast
Version 2017.1

Pneumonitis-Management PD1/ PDL1-Inhibitors

Guidelines Breast
Version 2017.1

I° (asymptomatic, CT-morphological changes)	Continue	If necessary follow up by imaging
II° (oligosymptomatic, coughing/ dyspnea on exertion)	Discontinue	oral 0,5-1 mg/kg BW methylprednisolone* †
III° (dyspnea at rest , ADL-limitation, oxygen need)	Discontinue	i.v. 1-2 mg/kg BW methylprednisolone † ‡
IV° (life threatening, Indication for tracheo-tomy / intubation)	Discontinue	i.v. 1-2 mg/kg BW methylprednisolone, evtl. after 48-72h + Infliximab/ MMF/ Endoxane ‡

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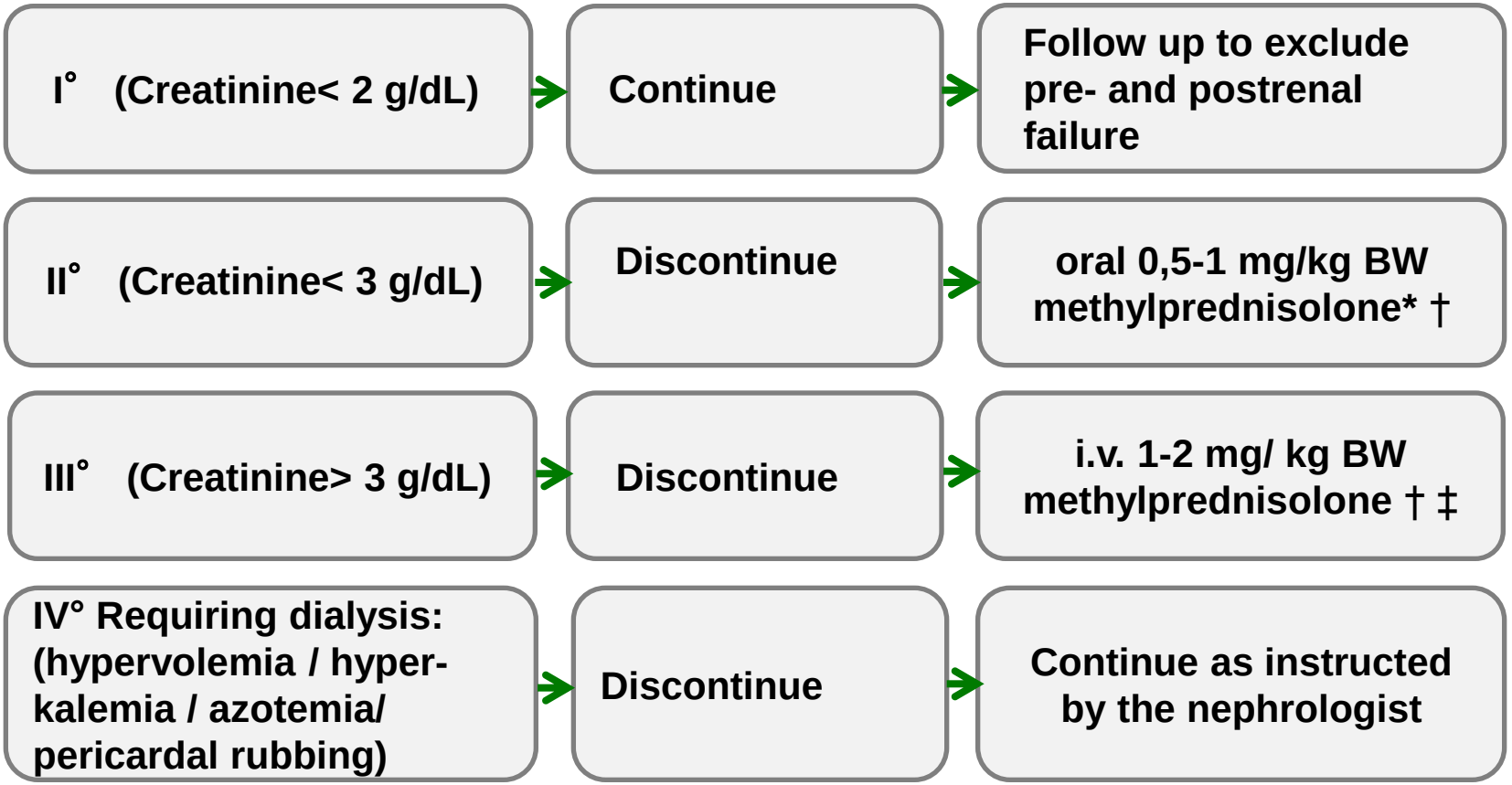
*** Prophylactic antibiotics using ciprofloxacine 500 mg bid p.o., Prophylaxis against gastric ulcer using PPI, oral potassium substitution. If no improvement treatment like pneumonitis grade III**
† If improvement, steroids can be deescalated over 1 month
‡ Any Pneumonitis ≥ grade III bronchoscopy using BAL/ with sampling

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

Nephritis-Management PD1/PDL1-Inhibitors



* * Prophylactic antibiotics using ciprofloxacine 500 mg bid p.o., Prophylaxis against gastric ulcer using PPI, oral potassium substitution. If no improvement treatment like pneumonitis grade III
† If improvement, steroids can be deescalated over 1 month
‡ Starting from nephritis grade III counselling nephrology to obtain tissue samples

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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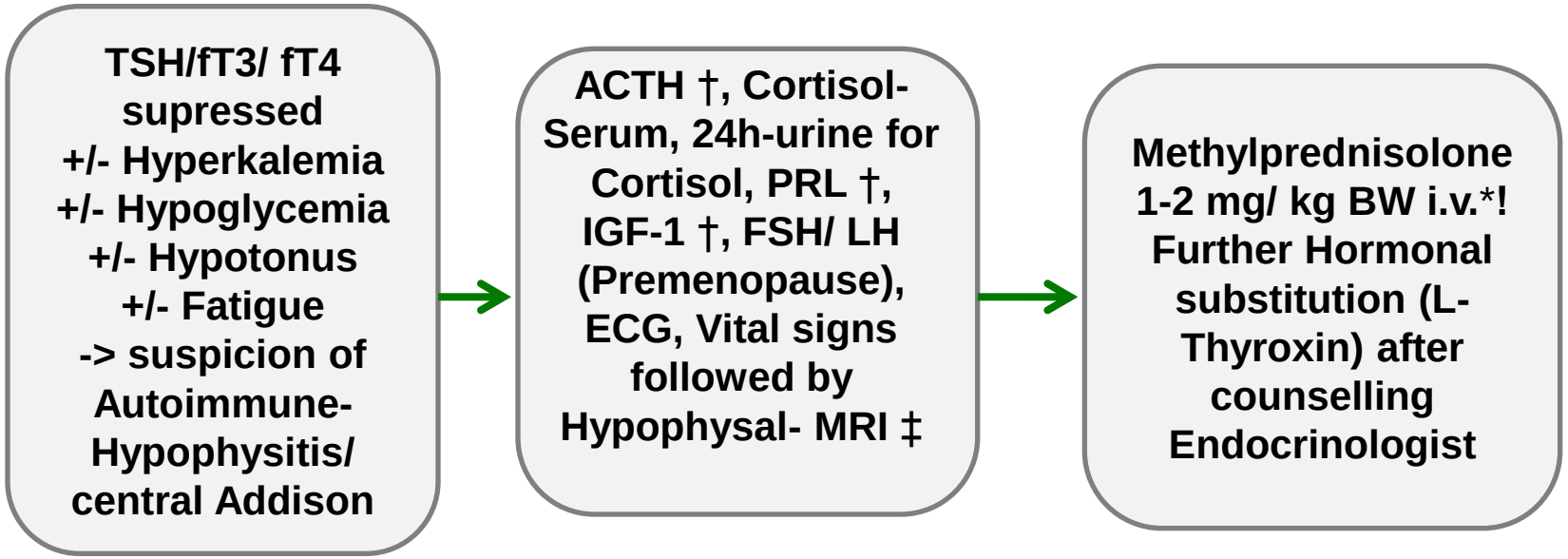
Hypophysitis-Management PD1/ PDL1-Inhibitors



† ACTH: adrenocorticotropal hormone, PRL: Prolactin, IGF-1: insulin growth factor-1
‡ Hypophysal-MRI after counselling neuroradiologist
* Stop treatment with Checkpoint-Inhibitors, prophylactic antibiotics with Ciprofloxacin 500 mg bid p.o., gastric ulcus prophylaxis with PPI, oral Potassium substitution.
Deescalate Methylprednisolone (reduced bioavailabilty of oral steroids), if Methylprednisolone 8 mg/d p.o. -> change to Hydrocortisone maintenance therapy (15-10-5 mg daily); no ACTH- controls
Addison-emergency pass; -> if stress (fever, deterioration of condition) increase dose to 45-30-15 mg tgl.
Continue treatment with Checkpoint-Inhibitors after clinical judgement

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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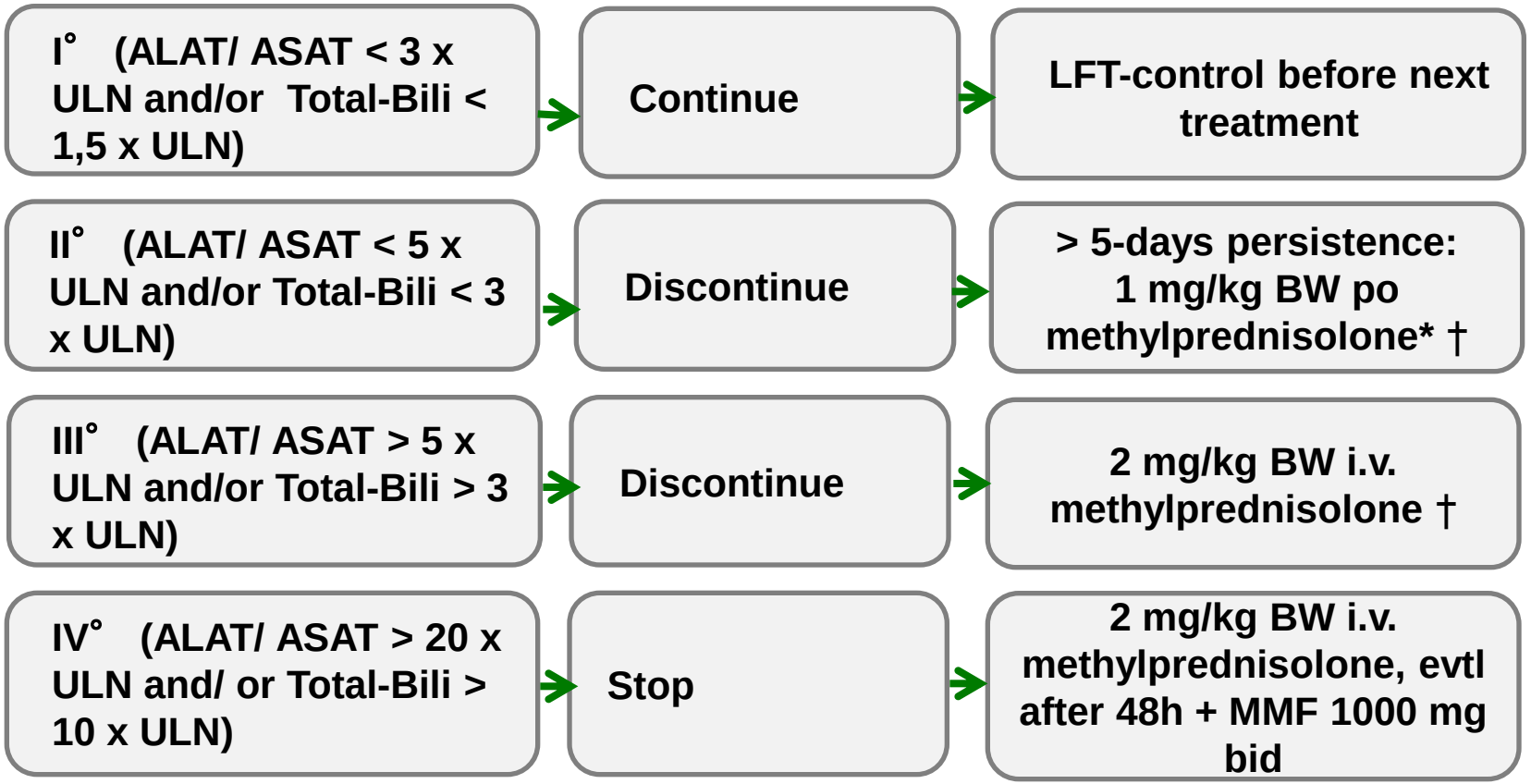
Further Information

References

Hepatitis-Management PD1/ PDL1-Inhibitors



*** Prophylactic antibiotics with ciprofloxacine 500 mg bid p.o., gastric ulcer prophylaxis with PPI, oral potassium substitution. Reduced bioavailability of oral steroids, if no amelioration treat like Hepatitis III°**
† Sonography / CT Abd., HBV-/ HCV-/ CMV-/ EBV Serolog, IG-Elektrophoresis, ANA, ANCA, ASMA, AMA, anti-LKM1, anti-SLA, evtl liver biopsy. If amelioration, reduce to 1 mg/kg BW methylprednisolone i.v. (2 weeks followed by Steroid-Tapering (1 month), Start with PD1/ PDL1 Inhibitors when 10 mg/d prednisolone (8 mg/d methylprednisolone)

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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Colitis-Management PD1/ PDL1-Inhibitors

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Diarrhea I° (< 3 x day)	Continue	Symptomatic treatment (Loperamide)
Diarrhea II° (4-6 x day)	Discontinue	> 5-days persistence: 1 mg/kg BW po methylprednisolone*
Diarrhea III° (7-10 x day)	Discontinue	2 mg/kg BW i.v. methylprednisolone †
Diarrhea IV° (>10 x day)	Stop	2 mg/kg BW i.v. methylprednisolone + evtl infliximab 5 mg/kg BW ‡

* Microbio dg (C-diff. exclusion). Prophylactic antibiotics with ciprofloxacin 500 mg bid p.o., gastric ulcer prophylaxis with PPI, oral potassium substitution. Reduced bioavailability of oral steroids: if no amelioration, treat like Diarrhea III°

† Coloscopy with sampling, CT-Abdomen if left Colitis (Diverticulitis-exclusion). If amelioration reduce to 1 mg/kg BW methylprednisolone i.v. (2 weeks) followed by Steroid-Tapering (1 month), Start with PD1/ PDL1 Inhibitors when 10 mg/d prednisolone (8 mg/d methylprednisolone)

‡ pretherapeutic HBV/ HCV/ CMV/ Tb-(Quantiferon) Serology, infliximab contraindicated if perforation/ sepsis; Apply 2h i.v. with 1,2 µm Filter (up to15% infusion reactions), evtl repeat day 15

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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Thyroiditis-management PD1/PDL1-inhibitors

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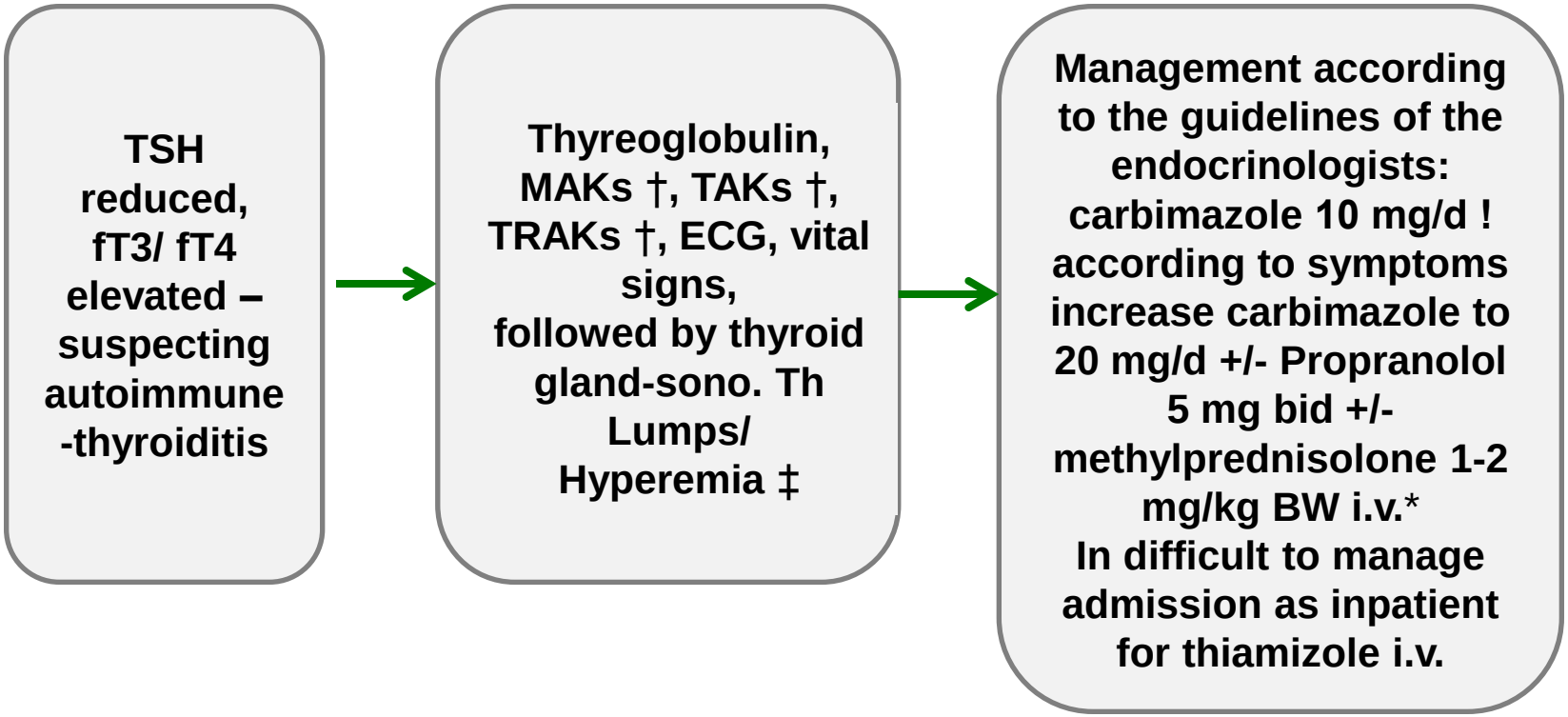

† MAKs: anti-TPO antibdoes, TAKs: anti-thyroglobulin-antibodies, TRAKs: anti-TSH-receptor-antibodies
‡ Thyroid gland sonography in endocrinology-outpatient clinic, refer
! With carbimazol discontinue therapy using checkpoint-inhibitors and weekly follow-ups of TSH/ fT3/ fT4/CBC, ALAT/ ASAT/ AP, continue treatment only if fT3/ fT4 are falling
* Prophylactic antibiotic using ciprofloxacine 500 mg bid p.o., gastric ulcer prophylaxis using PPI, oral potassium substitution, continue the management using checkpoint-inhibitors and oral methylprednisolone. N.B.: reduced bioavailabitiy of oral steroids

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017

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References

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Toxicities of New Drugs

Häufigste Nebenwirkungen im Verlauf einer Langzeit-Therapie mit Palbociclib in PALOMA-1

	Therapiedauer				
UE, %	**0 ≤ 6 Monate (n = 95)**	**6 ≤ 12 Monate (n = 77)**	**12 ≤ 18 Monate (n = 59)**	**18 ≤ 24 Monate (n = 40)**	**≥ 25 Monate (n = 29)**
Jegliche UE	97,9	88,3	81,4	72,5	79,3
Neutropenie	69,5	54,5	44,1	40,0	51,7
Leukopenie	33,7	27,3	16,9	20,0	13,8
Fatigue	33,7	14,3	13,6	10,0	10,3
Übelkeit	23,2	6,5	5,1	2,5	6,9
Anämie	22,1	19,5	15,3	15,0	13,8
Diarrhoe	18,9	0	5,1	2,5	10,3
Alopezie	16,8	2,6	1,7	0	3,4
Hitzewallung	16,8	7,8	0	0	0
Gelenkschmerzen	12,6	10,4	15,3	7,5	13,8
Dyspnoe	12,6	2,6	6,8	0	3,4
Appetitminderung	10,5	7,8	0	2,5	0
UE: unerwünschtes Ereignis					

N. Harbeck, J.Ettl, Drug Report, 2017

Monitoring Palbociclib

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Further Information

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Mögliche Neutropenie unter Palbociclib: Monitoring und Dosisanpassung	
Vor Beginn der Behandlung und zu Beginn jedes Zyklus sowie am 14. Tag der ersten 2 Behandlungszyklen und sofern klinisch indiziert, sollte eine Kontrolle des großen Blutbildes erfolgen.	
Hämatologische Toxizitäten	
CTCAE-Grad (Neutrophilenzahl)	**Dosisanpassungen**
Grad 1 (< unterer Grenzwert bis 1500/ml) **Grad 2** (1000 bis ≤ 1500/µl)	keine Dosisanpassung erforderlich
Grad 3[a] (500 bis < 1000/µl)	1. Tag des Zyklus: **Therapiepause** bis ≥ 1000/µl Neutrophilie wieder erreicht sind, nach 1 Woche erneute Blutbildkontrolle. Bei ≥ 1000/µl Neutrophilie den nächsten Zyklus in gleicher Dosierung beginnen. 14. Tag der ersten 2 Zyklen: Palbociclib mit aktueller Dosierung bis Zyklusende fortsetzen. Am 21. Tag erneute Blutbildkontrolle. Bei Grad-3-Neutropenie > 1 Woche oder rezidivierender Grad-3-Neutropenie Dosisreduktion in nachfolgenden Behandlungszyklen erwägen.
Grad 3 (500 bis < 1000/µl) + Fieber ≥ 38,5 °C und/oder Infektion	**Therapiepause** bis ≥ 1000/µl Neutrophilie. Wiederaufnahme mit 1 Dosisstufe niedriger.
Grad 4[a] (< 500/µl)	**Therapiepause** bis ≥ 1000/µl Neutrophilie. Wiederaufnahme in der nächst niedrigeren Dosisstufe.

N. Harbeck, J.Ettl, Drug Report, 2017

Guidelines Breast
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Adverse Effects of Olaparib

Adverse effects (AE):	Grade and occurence	Management
Gastrointestinal AE (Nausea, vomiting, diarrhea):	- mostly gr. 1-2, - no prophylactic antiemetics necessary	- interruption / - dose reduction - antiemetics
Hematological AE (anemia, leucopenia, thrombocytopenia):	- mostly gr. 1-2, - CBC at the start and monthly (in the first 12 montlhs	- interruption / - dose reduction - if nec. GCSF, transfusion
Neurological system (headache, dizziness):	- mostly gr. 1-2,	- interruption / - dose reduction
Metabolism / Diet (reduced appetite):	- mostly gr. 1-2,	- interruption / - dose reduction

Therapy Side Effects (2/35)

Further information:

Screened data bases: Pubmed 2007 - 2017, ASCO 2010 – 2016, SABCS 2010 – 2016, Cochrane data base (2016)

Screened guidelines:
NCI (National Cancer Institute , 2016): http://www.cancer.gov
ASCO (American Association of Clinical Oncology, Practice Guidelines, 2016) http://www.asco.org
CMA (Canadian Medical Association , 2016): http://www.cmaj.ca
NCCN (National Comprehensive Cancer Network , 2016): http://www.nccn.org
S3 Leitlinie Supportive Therapie, November 2016

No references

Toxicity Assessment (3/35)

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.
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Acute Toxicity (NCI CTCAE vs 4.03 2010) (4/35)

No further information

No references

Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (5/35)

No further information

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Cytotoxic Anti-Cancer Drugs – Acute Toxicity II (6/35)

No further information

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See slide 5

Peripheral Neuropathy (7/35)

No further information

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Chemotherapy Induced Peripheral Neuropathy (8/35)

No further information

No references

Long-Term Toxicity Cardiotoxicity I (9/35)

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 asymptomatc 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 cardiotoxcity 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- (antihormontherapy 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 comorbities 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 (10/35)

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. Simultaneusly 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/Pertuzumab: Algorithm in Case of Cardiac Toxicity (11/35)

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 trastucumab 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 (12/35)

Further information:

Approximately one in every 20 breast cancer patients deveolped 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 occurance 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%CI1.46 to 8.04), chemotherapy with increased risk of melanoma, uterine cancer, acute myeloid leukemia and homonal 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 femal Australien population, with highest age-specific relative risk for AML in the 30- to 49-age group.[1]
Mitoxoantrone-based chemotherapy was associated with a higher leukemic risk than with anthrazyclines (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 leucemia/MDS was significantly elevated.[3]
Granulacyte 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 myelogeneous 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 mg2 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 (after Radiotherapy) (13/35)

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 beem 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) (14/35)

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 oftenly 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 dissease-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 differnces.[4]

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(Therapy Related) Fatigue (15/35)

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-κB 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 (Bruerat 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 glucocorticoides, which are used broadly in daily praxis, has not yet been evaluated.

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(Therapy Associated) Sleeping disturbance (16/35)

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 (17/35)

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). Antidepressents 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 (18/35)

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. 2007Stewart 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, are there 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 (19/35)

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 occurence 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 Modyfing Agents (BMA, Bisphosphonates, Denosumab) (20/35)

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 (21/35)

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) (22/35)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 20-21/35!

Key-Toxicities Antibodies/Antibody-drug-conjugates – Small Molecules (23/35) and (24/35)

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 tysosinkinase-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 bavcizumab 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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No further information

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Ribociclib

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Everolimus

1. Jerusalem G, Mariani G, Ciruelos EM, Martin M, Tjan-Heijnen VC, Neven P, Gavila JG, Michelotti A, Montemurro F, Generali D, Simoncini E, Lang I, Mardiak J, Naume B, Camozzi M, Lorizzo K, Bianchetti S, Conte P. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or

metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol. 2016 Sep;27(9):1719-25. doi: 10.1093/annonc/mdw249. Epub 2016 Jun 29.

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2. Hong S, Funchain P, Haddad A, Crowe J, Dalpiaz N, Abraham J. Complete Durable Response From Carboplatin and Olaparib in a Heavily Pretreated Triple-Negative Metastatic Breast Cancer With Germline BRCA2 and "BRCAness" Mutations. J Oncol Pract. 2016 Mar;12(3):270-2. doi: 10.1200/JOP.2016.010710.

Neratinib

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Pneumonitis-Management PD1/PDL1-Inhibitors (27/35)

No further information

No references

Nephritis-Management PD1/PDL1-Inhibitors (28/35)

No further information

No references

Hypophysitis-Management PD1/PDL1-Inhibitors (29/35)

No further information

No references

Hepatitis-Management PD1/PDL1-Inhibitors (30/35)

No further information

No references

Colitis-Management PD1/PDL1-Inhibitors (31/35)

No further information

No references

Thyroiditis-Management PD1/PDL1-Inhibitors (32/35)

No further information

No references

Toxicities of New Drugs (33/35)

No further information

No references

Monitoring Palbociclib (34/35)

No further information

No references

Adverse effects of Olaparib (35/35)

No further information

No references

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Supportive Care

START

Supportive Care

- **Version 2002:**
  Diel

- **Versions 2003–2016:**
  Bauerfeind / Bischoff / Costa / Dall / Diel / Fersis / Hanf / Heinrich / Jackisch / von Minckwitz / Möbus / Oberhoff / Rody / Schaller / Scharl / Schmidt / Schütz

- **Version 2017:**
  Möbus / Nitz

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Guideline Spectrum

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients

Without claiming completeness, such guidelines will be quoted, with an emphasis on German guidelines.

Aspects concerning breast cancer patients will especially be highlighted.

The „Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG: http://www.onkosupport.de“ should especially be highlighted.

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

„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

Erythropoiesis-stimulating agents (ESAs)

	Oxford / LoE / GR		AGO
➢ Indicated in asymptomatic anaemia	1a	B	-
➢ Therapy and secondary prophylaxis in CIA	1a	A	+
➢ In the adjuvant setting	1b	A	+
➢ In the neoadjuvant/metastatic setting	1a	A	+/-
➢ In dose-dense / dose-escalated CT (iddETC)	1b	A	+
➢ Treatment start at Hb-levels < 10 g/dL	1a	A	+
➢ Target Hb 11–12 g/dL	1a	A	+
➢ Improvement of outcome (DFS, OS)	1a	B	--
➢ Risk of thromboembolic events is increased by use of ESAs	1a	A	

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References

Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

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N=2.098 Pat., Hb <11g/dl; non inferiority study.
Prespecified upper non inferiority margin = 1.15

	PFS (median)		OS (median)	ORR	RBC transfusions	TVE
Epo	Invest.* 7,4 Mon	IRC** 7,6 Mon	17,2 Mon	50%	5,8%	2,8%
BSC	7,4 Mon.	7,6 Mon.	17,4 Mon	51%	11,4%	1,4%
	HR: 1,09	HR: 1,02	HR: 1,06	OR: 0,95	p<.001	p=.04
	Upper CI: 1,20	Upper CI: 1,146				

* Investigator determined
**Independent review committee

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References

Practical Use of ESAs

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- **Epoetin α and Darbepoetin are equieffective**
- **Dosage:**
  - **Epoetin α: 150 IU/kg 3 x weekly s.c. or**
    40.000 IU 1 x /week s.c. or
    80.000 IU q2w s.c. or
    120.000 IU q3w s.c.
  - **Epoetin ß: 30.000 IE weekly s.c.**
  - **Darbepoetin: 2,25 µg/kg s.c. weekly or 500 µg s.c. q3w**
- **Hematologic blood samples weekly**
  - **Dose reduction if Hb-increase > 1g/dl within 2 weeks**
  - **Dose increase if Hb-increase < 1g/dl within 4-6 weeks**
- **In case of FID (“functional iron deficiency”) iron supplementation, preferably i.v.**
- **Stop ESA-treatment if there is no Hb increase after 9 weeks**

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Further Information

References

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**
- **Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist 2008;13(Suppl):33–36.**

Granulocyte Colony-stimulating Factors

Guidelines Breast
Version 2017.1

	Oxford / LoE / GR	AGO	
➢ **Primary prophylaxis for expected febrile neutropenia (FNP)**			
➢ **If expected risk for FNP 10–20%**	1b	B	+/-
➢ **In case of individual risk factors**	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 10^9**	1b	A	++

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: 04/07)

Definition (oral temperature of >38.5° C or two consecutive readings of >38° C for 2 h in a patient with an ANC of <500 cells/mm³ or expected to fall to <500 cells/mm³)

	Oxford / LoE	GR	AGO
➢ 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	+/-

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References

Empirical Antibiotic Therapy

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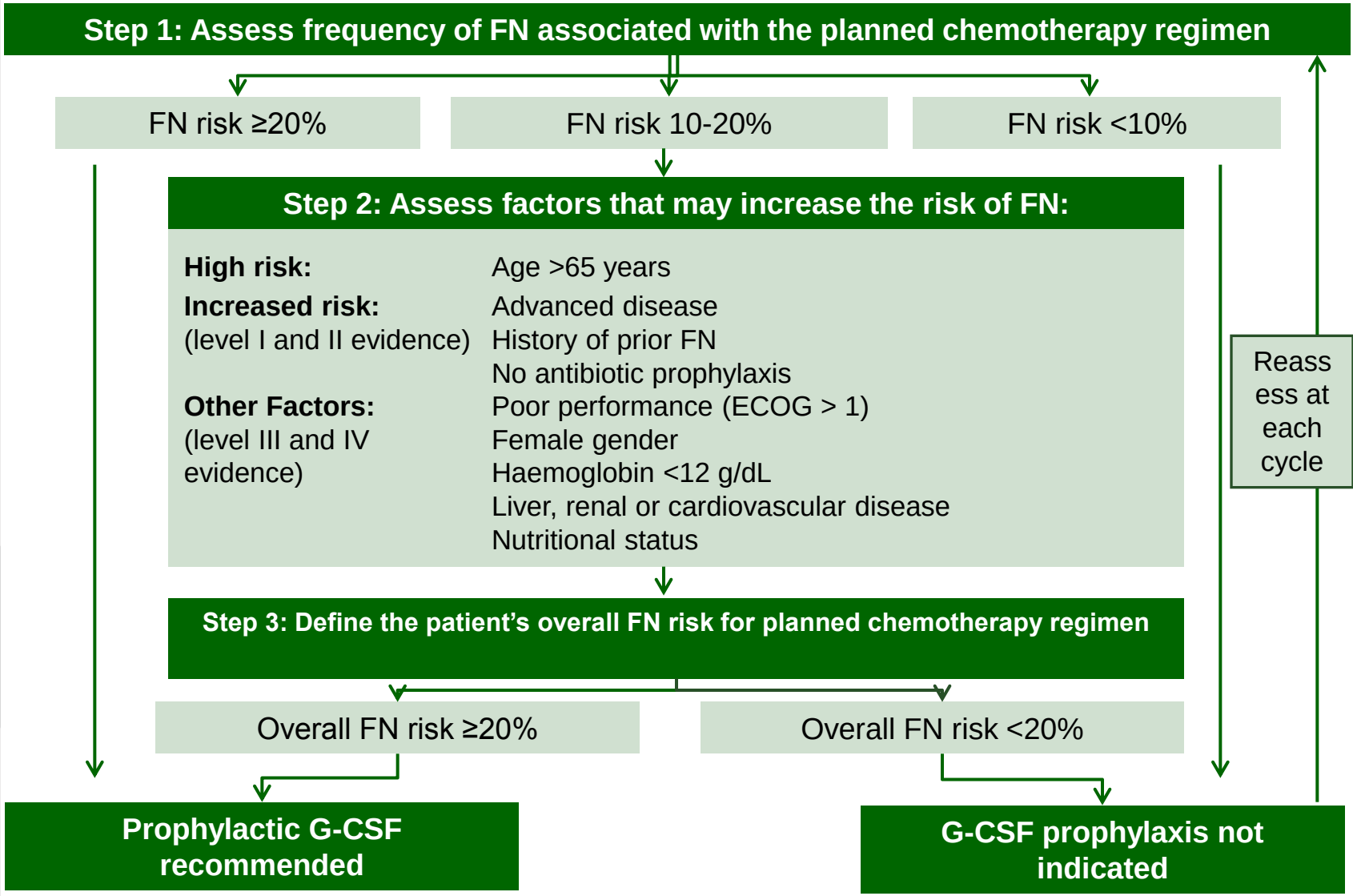
The recommendations for empirical antibiotic therapy are currently changing because of infection biological findings. Current recommendations should be referred to regularly and adjusted to within personal professional judgement.

The “Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de“ is a source for regular consultation.

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



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Further Information

References

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Relevant Guidelines

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- 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

Prophylaxis of Infections

rarely applicable to Patients with Solid Tumors (e.g. BC)

ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

	Oxford / LoE	/ GR	AGO
➢ 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: estimated duration of neutropenia < 100/µl ≤ 7d**

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Further Information

References

Mucositis Prevention

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

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

Oxford / AGO
LoE / GR

- **Standardised mouth hygiene for prophylaxis of oral mucositis should be adhered to by all age groups and during all cancer-related therapies with any risk for oral mucositis.**

2b ++

This entails:

1)patient:

- **Regular mouth washs (H_2O, NaCl)**
- **Soft tooth brushs**
- **Interdental care: flossing or using interdental brush**
- **Avoidance of alcohol, tabac, hot food, sour food**
- **Regular screening for lesions**

2) Risk adjusted prophylaxis by dentician

3) Continuous clinical control

Mucositis

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

- **Desinfecting / antiphlogistic measures**:
  Mouth rinsing with infusions of chamomile or salvia, extracts of chamomile, 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-mouth gel®) 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, Doxepin 0,5% p.o.
- **Pain Therapy:** Opioids if indicated

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Paravasates with Potentially Necrotising Substances (Anthracycline, Taxane, Vinorelbin)

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	Oxford / LoE / GR	AGO	
➢ **Dexrazoxane for treatment of Anthracyclin-Paravasates (exception: liposomal A)**	2b	B	++
➢ **Hyaluronic Acid for treatment of Taxan/Vinorelbin-Paravasates**	3b	D	++

Paravasation Dexrazoxane/Hyaluronic Acid

Dexrazoxane for treatment of anthracyclines paravasates

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.**

Hyaluronic Acid in case of Taxan/Vinorelbin Paravasates:

- **1-10 Amp a 150 IU**
- **1 ml dissolvent (z.B. NaCl 0.9%)**
- **Local anaesthesia**
- **No thermotherapy after taxanes**
- **Dry warmth 4 x daily 20 min during vincaalkaloids**

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References

Antiemetic Therapy

http://www.mascc.org/antiemetic-guidelines
www.onkosupport.de

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	Oxford / LoE	GR	AGO
➢ 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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Further Information

References

Supportive Therapy
Antiemetics

Guidelines Breast
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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, Aaapro 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 Therapy Antiemetics

Substance group	Substance	Dosage	Side effects	Potential
Serotoninantagonists	Ondansetron Tropisetron Granisetron Palonosetron	8 mg i.v., 2 x 4-8 mg p.o, transdermal 5 mg i.v., 5 mg p.o. 1-3 mg i.v. 0, 25 mg i.v.	Headaches. Diarrhea, flush symptome, increase of transaminases, intestinal atony at high dosages.	Very high
NK1-Antagonists	Aprepitant Fosaprepitant	125 mg d1, 80 mg d 2-3 p.o. 150 mg d1 i.v.	Cytochrom-P-450-activation with dose reduction of Dxamethasone (2 x 8 mg). Do not combine with Astemizol, Terfenadin, Cisaprid	Very high
Dopaminantagonists/ substituted Benzamids	Metoclopramid Alizaprid	up to 120 mg/24h as a steady infusion or as drops up tp 300 mg i.v. or p.o./24 h (6 Amp. od. 6 tbl.)	Dyskinesia (Antidot:Biperiden) Anxiousness, Depression, Diarrhea	High
Phenothiazins/ Butyrophenons	Haloperidol	1-3 mg 4 x/d	Sedation, Cramps, transient increase of biochemical liver function values	Moderate
Corticosteroids	Dexamethason Prednisolon	8-20 mg i.v. 1-3 x/d 100-250 mg i.v. 1-3 x/d	Extreme blood sugar values, psychotic reactions, flush syndrome, Hypertension	Moderate
NEPA (Netupitant and Palonosetron)	fixed combinations (oral)	NE 300 mg PA 0,5 mg		Very high

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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), fentanyle (transdermal), hydromorphone, oxycodone, as a back-up levomethadone. The dose of opioids should be titrated step by step according to the analgetic effect.
- **Additional drugs – „adjuvants“**
  Gabapentine, pregabaline, carbamazepine, amitriptyline, bisphosphonats

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References

Diarrhea

- **Adsorbent agents**
  - Carbo medicinalis*; caoline / pectine, Al-Mg-silicate hydrate*
- **Analgetics, opioids**
  - Loperamide; c*odeine, morphine IV, tinctura opii, butylscopolamine*
- **Colitis pseudomembranosa**
  - Metronidazols *or (if not effective) vancomycine*

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Constipation
Important Side Effect of Opioid Treatment

- **Bulging agents**
  - Psylium, 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

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References

Skin toxicities

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
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	Oxford / LoE / GR	AGO
➢ Avoidance of chemotherapy-induced alopecia by cooling the patient‘s scalp*	1b	+/-
➢ Prophylaxis of hand-foot-syndrome using urea containing lotions (5-10%)	1b	+
➢ Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel	2b	+

*Substance- and regimen specific

Scalp Cooling Alopecia Prevention trial (SCALP)

J Clin Oncol 34, 2016 (suppl; abstr TPS10144) Nangia JR, Wang T, Niravath PA et.: Scalp Cooling Alopecia Prevention trial (SCALP) for patients with early stage breast cancer

<u>Design</u>
Randomized trial, scalp cooling device vs. control

Assessed for: alopecia, quality of life, device safety

<u>Results</u>
Primary Outcome: hair preservation

Cooling: 50.5 % success vs. 49.5 % failure
Non-cooling: 0 % success vs. 100 % failure

Fisher's exact test $p < 0.001$

Prevention of CIPN

(chemotherapy induced peripheral polyneuropathia)
Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

	Oxford / LoE / GR	AGO
➢ Physical activity reduces the functional losses	5	+
➢ There is no effective prevention of CIPN	1b	--
➢ Alpha-liponic acid	1b	--
➢ Amifostine	1a	--
➢ Carbamazepine	1b	--
➢ Vit E	1a	--
➢ L-Carnitine	1b	--

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Therapy of CIPN

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

	Oxford / LoE / GR	AGO
➢ Physical Therapy	5	+
➢ Duloxetine for pain induced by CIPN	1b	+
➢ Gabapentine	1b	+
➢ Amitryptiline	1b	+
➢ Venlafaxine	5	+
➢ Pregabaline	5	+
➢ Lamotrigine	1b	-
➢ Opioids for treatment of CIPN-induced pain	5	+
➢ Capsaicine / Lidocaine locally	5	+
➢ Menthol locally (1%)	5	+
➢ Baclofene		

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 (2/28)

No further information

No references

Guideline spectrum (3/28)

No further information

No references

Erythropoesis-Stimulating Agents (ESAs) (4/28)

No further information

References:

1. Mountzios G, Aravantinos G, Alexopoulou Z et al.: Lessons from the past: Long-term safety and survival outcomes of a prematurely terminated randomized controlled trial on prophylactic vs. Hemoglobin-based administration of erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia. Molecular and clinical oncology 4: 211-220, 2016.
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6. Moebus V, Jackisch C, Schneeweiss A et al.: Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer. Randomized clinical trial. J Natl Cancer Inst; 2013; 105: 1018-1026.
7. Swain SM, Tang G, Geyer CE Jr, et al. 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; 31: 3197-3204.
8. Untch M, Fasching PA, Konecny GE, 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

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Practical use of ESAs (6/28)

No further information

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Granulocyte Colony-stimulating Factors (8/28)

No further information

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Empirical Antibiotic Therapy (10/28)

No further information

No references

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No further information

No references

Relevant Guidelines (12/28)

No further information

No references

Prophylaxis of Infections (13/28)

No further information

No references

Mukositis Prevention (14/28)

No further information

No references

Mucositis (15/28)

No further information

No references

Paravasates with Potentially Necrotising Substances (Anthracycline, Taxane, Vinorelbin) (16/28)

No further information

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Paravasation Dexrazoxane/Hyaluronic Acid (17/28)

No further information

No references

Antiemetic Therapy (18/28)

No further information

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Supportive Therapy Antiemetics (19/28)

No further information

No references

Supportive Therapy Antiemetics (20/28)

No further information

No references

Analgesia (21/28)

No further information

References:

Relevant practice guideline:
Deutsche Gesellschaft zum Studium des Schmerzes, www.dgss.org

Diarrhea (22/28)

No further information

No references

Constipation- Important Side Effect of Opioid Treatment (23/28)

No further information

No references

Skin toxicities (24/28)

No further information

References:

Relevant practice guideline:

Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

Scalp Cooling Alopecia Prevention trial (SCALP) (25/28)

No further information

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Prevention of CIPN, (chemotherapy induced peripheral polyneuropathia) (26/28)

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Therapy of CIPN (27/28)

No further information

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Relevant practice guideline:

1. Multidisciplinary S 3 guidelines of the AWMF (Reg.-Nr. 032-054OL):
„Supportive Therapie bei onkologischen PatientInnen - interdisziplinäre Querschnittsleitlinie“, released 11.11.2016

Palliative Care (28/28)

No further information

No references

Guidelines Breast
Version 2017.1

Breast Cancer:
Specific Situations

START

Breast Cancer: Specific Situations

Guidelines Breast
Version 2017.1

- **Versions 2005-2016:**
  Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Rody / Scharl / Schneeweiss / Solomayer / Thomssen
- **Version 2017:**
  Schütz / Sinn

Guidelines Breast
Version 2017.1

Breast Cancer: Specific Situations

- **Young patients**
- **Pregnancy- and breast-feeding-associated BC**
- **Elderly patients**
- **Male patients**
- **Inflammatory BC**
- **Occult Breast Cancer (Cancer of unknown primary – axillary CUP)**
- **Paget‘s disease**
- **Malignant and Borderline Phyllodes Tumor**
- **Angiosarcoma**
- **Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)**

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Guidelines Breast
Version 2017.1

Breast Cancer in Young Women ≤ 35 Years

	Oxford / AGO LoE	GR	
➢ Aggressive biological behavior with worse prognosis	2a	B	
➢ Surgery like patients ≥ 35 y	2b	B	+
➢ Guidelines adapted (neo-)adjuvant systemic treatment (see chapters there)	1b	A	++
➢ GnRHa as ovarian protection (see chapter gyn. problems)	1b	B	+
➢ Genetic and fertility counseling	2b	B	++
➢ Contraception counseling	2b	B	++

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Version 2017.1

Breast Cancer During Pregnancy*
or Breast Feeding – Diagnostics and Surgery

	Oxford / AGO LoE	GR	
➢ Breast imaging & biopsy like in non-pregnant	4	C	++
➢ Staging if indicated (Bone scan after delivery)	5	D	+
➢ Surgery like in non-pregnant patients	4	C	++
➢ Sentinel node excision (technetium only)	4	C	+
➢ SLNE during 1st trimester	5	D	+/-
➢ Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs	4	C	++
➢ Blue dye (has not been tested in pregnant animals or humans)	4	C	--

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Breast Cancer During Pregnancy
- (Neo-)adjuvant Therapy -

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR		
➢ Radiation therapy during pregnancy	4	C	-
➢ (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)			++
➢ ➢ Anthracyclines: AC, EC	2b	B	++
➢ ➢ Taxanes	2b	B	+
➢ ➢ MTX (e.g. CMF)	4	D	--
➢ ➢ Endocrine treatment	4	D	--
➢ HER2-neu targeted treatment	3a	C	--
➢ Bisphosphonates, denosumab	4	D	-

Breast Cancer During Pregnancy*
- Delivery and Breast-Feeding-

Guidelines Breast
Version 2017.1

	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 last cycle of chemotherapy	4	C	++
➢ If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities	5	D	++

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Breast Cancer and Pregnancy
- Family Planning-

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ After breast cancer diagnosis reproductive techniques can be used to induce pregnancy	5	D	++
➢ Success rates for getting pregnant and for deliver a child are lower in breast cancer patients in comparison to non-cancer patients	5	D	++
➢ Breast cancer patients of reproductive age should be offered a fertility counseling before starting any kind of treatment	5	D	++
➢ Breast cancer patients should not be advised against getting pregnant regardless of tumor‘s hormone receptor status	5	D	++

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Pregnancy Associated Breast Cancer*: Outcome

Guidelines Breast
Version 2017.1

	Oxford LoE
➢ **BC during pregnancy / lactation**	
➢ Adequate treatment is essential	3a
➢ **Pregnancy and lactation after BC**	
➢ Outcome not compromized	3a

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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)

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Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

	Oxford / AGO LoE / GR		
➢ **Clinical geriatric assessment**	2b	B	++
➢ **Treatment according to guidelines**	2a	C	++
➢ **Surgery similar to „younger“ age**	2b	B	++
➢ **Endocrine treatment (endocrine resp.)**	1a	A	++
➢ **Chemotherapy (standard regimens)**			
➢ **< 70 years**	1a	A	+
➢ **> 70 years (especially N+, ER/PgR-)**	2a	C	+*
➢ **Radiotherapy**	1a	A	+
➢ **Omit radiotherapy after BCT in low risk with endocrine treatment**	1b	B	+
➢ **Trastuzumab**	2b	C	+

*Study participation recommended

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References

Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ **Reduced standard treatment**	2b	C	++
➢ **Options extrapolated from trials in elderly:**			
➢ No breast surgery (consider endocrine options)	2b	C	+
➢ No axillary clearing (≥ 60 y, cN0, rec.-pos)	2b	B	+
➢ No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)	1b	B	++
➢ Hypofractionated radiotherapy	2b	B	+
➢ No chemotherapy if >70 years and negative risk-benefit analysis	2b	C	+

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Version 2017.1

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	++
➢ **Screening for 2nd malignancies according to guidelines**	GCP		++

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Male Breast Cancer: Systemic Therapy

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ Adjuvant chemotherapy as in women	2a	B	++
➢ HER2-targeted therapy	5	D	+*
➢ Endocrine therapy	4	D	++
- Tamoxifen	2b	B	++
- Aromatase inhibitors (adjuvant)	2b	B	-*
- Aromatase inhibitors (metastatic BC)	4	C	+/-
- GnRHa and AI (metastatic BC)	4	C	+*
- Fulvestrant (metastatic BC)	4	C	+/-
➢ Palliative chemotherapy as in women	4	C	++

*Participation in register study recommended

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References

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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

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Further Information

References

Inflammatory Breast Cancer (IBC, cT4d)

	Oxford / AGO LOE / GR		
➢ **Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d**			++
➢ **Staging**	2c	B	++
➢ **Skin punch biopsy (at least 2; detection rate < 75%)**	2c	B	+
➢ **Neoadjuvant chemotherapy (regimens as in non-inflammatory BC)**	2c	B	++
➢ **Adjuvant systemic treatment according to guidelines**	2c	B	++
➢ **Mastectomy after chemotherapy**	2c	B	++
➢ **Breast conserving therapy in case of pCR (individual)**	2b	C	+/-
➢ **Sentinel excision only**	3b	C	-
➢ **Radiotherapy (PMRT)**	2c	B	++

Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

Guidelines Breast
Version 2017.1

- **Incidence: < 1% of metastatic axillary disease**
- **In > 95% occult breast cancer, < 5% other primary**
- **Immunhistology**
  - **ER-positive: 55%**
  - **HER2 3+: 35%**
  - **Triple-negative: 38%**
- **Nodal status:**
  - **1 - 3 Ln-Met. in 48%**
  - **> 3 Ln-Met in 52%**
- **Outcome similar or better than in breast cancer with similar tumor biology and tumor stage**

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Further Information

References

Axillary Metastasis in Occult Breast Cancer (Axillary CUP)

Imaging Diagnostics

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Mammography, Breast-ultrasound, Breast-MRI	3	B	++
➢ Exclude contralateral cancer	3	B	++
➢ Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)	5	D	++
➢ Staging (CT thorax / abdomen, thyroid scintigraphy, HNT-exam)	3	B	++
➢ PET / PET-CT	3b	B	+

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Further Information

References

Axillary Metastasis in Occult Breast Cancer (Axillary CUP)

Pathology, Molecular Pathology

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ ER, PgR, HER2, GATA3	5	D	++
➢ Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.	5	D	++
➢ Gene expression profiling for determination or primary site (CUPprint, Pathwork, TOT, Theros CTID)	2c	B	+/-
➢ NGS, epigenetics for determination of primary site (Panel-Sequencing, EPICup)	2c	B	+/-
➢ Prognostic gene expression tests	5	D	- -

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References

Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Therapy

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Axillary dissection	3a	C	++
➢ Mastectomy if breast MRI is negative	3a	C	-
➢ (Neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO)	5	D	++
➢ 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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Further Information

References

Paget‘s Disease of the Breast

- **Paget‘s disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer. Isolated Paget‘s disease of the nipple is more rarely seen, and less aggressive.**

Feature	Frequency
Presentation	Paget‘s disease with invasive Ca. (37 - 58%) Paget‘s disease mit DCIS (30 - 63%) Isolated Paget‘s disease (4 - 7%) Isolated Paget‘s disease with invasion (rare)
IHC	HER2-positive (83 - 97%) ER-positive (10 - 14%) AR-positive (71 - 88%)

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References

Paget‘s Disease of the Breast Diagnosis

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Histological verification by skin biopsy			++
➢ Mammography, sonography	4	D	++
➢ MR of the breast if other imaging negative	4	C	+
➢ Immunhistology (ER, PgR, HER2, Ck7) to detect benign and HER2-negative cases	5	D	++

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References

Paget‘s Disease of the Breast Therapy

	Oxford / AGO LOE / GR		
Paget‘ s disease with underlying disease (invasive breast cancer, DCIS)			
Therapy according to standard of the underlying disease	**5**	**D**	**++**
Surgery must achieve R0	**1c**	**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**	**- -**

Borderline and Malignant Phyllodes Tumor

- **Differential diagnosis may be problematic on core biopsy**
- **In-Breast recurrence relatively frequently seen (10 - 30%)**
- **Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.**

Feature	**Frequency**
Grading	Benign PT (75%) Borderline PT (16%) Malignant PT (9%)
Median age on diagnosis	Benign PT: 39 J. Borderline PT: 45 J. Malignant PT: 47 J.
Local recurrence	Benign PT: 10 - 17% Borderline PT: 14 - 25% Malignant PT: 23 - 30%

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References

Borderline and Malignant Phyllodes Tumor Diagnosis

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Mammography, sonography	3	C	++
➢ Diagnosis on core biopsy, grading on resection specimen	3	C	++
➢ Breast MRI	3	C	+/-
➢ Staging only malignant PT (CT thorax, skeletal system)	5	D	++

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Further Information

References

Guidelines Breast
Version 2017.1

Borderline and Malignant Phyllodes Tumor Surgery

	Oxford / AGO LOE / GR		
➢ R0-Excision	2b	B	++
➢ SNE / Axillary dissection when cN0	4	C	- -
➢ Treatment of local recurrence			
➢ R0 resection or simple mastectomy	4	C	++

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References

Guidelines Breast
Version 2017.1

Borderline and Malignant Phyllodes Tumor Adjuvant Therapy

	Oxford / AGO LOE / GR		
➢ Adjuvant radiotherapy	4	C	- -
➢ If T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)	2b	C	+/-
➢ Systemic adjuvant therapy (chemo, endocrine)	4	C	- -
➢ Treatment of local recurrence			
➢ R0 resection or simple mastectomy	4	C	++
➢ Radiotherapy, chemotherapy after R1 resection	4	C	+/-
➢ Distant metastases (very rare)			
➢ Treatment like soft tissue sarcomas	4	C	++

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Further Information

References

Sarcomas of the Breast

- **Not infrequently associated with familial syndromes (Li-Fraumeni, familial adenomatous polyposis, neurofibromatosis type 1)**
- **Primary sarcomas: angiosarcoma, undifferentiated sarcoma, leiomyosarcoma, liposarcoma, osteosarcoma**
- **Secondary malignancies of the breast:**
  - **Radiotherapy-Associated Angiosarcoma**
  - **Breast Implant Associated Large-Cell Anaplastic Lymphoma (BI-ALCL)**
- **Rare: intramammary sarcoma metastases**
- **Staging: TNM (UICC) or AJCC scheme of the soft tissue sarcoma analogous to sarcoma of the breast**
- **Grading: Analogous to the FNCLCC system for sarcoma or according to Rosen (1988) for angiosarcomas**

Primary Angiosarcoma of the Breast

- **Most common primary sarcoma of the breast**
- **Young age (median: 24 - 46 years)**
- **Indistinct tumor borders**
- **Large tumor (median: 5 - 7 cm)**
- **Uncharacteristic findings on mammography and sonography**
- **High local recurrence risk, even after mastectomy**
- **More unfavorable prognosis than other primary sarcoma of the breast**

Primary Angiosarcoma of the Breast* Diagnosis

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Mammography, sonography to determine extent of disease	3a	C	--
➢ Preoperative MRI to determine the extent of disease	3a	C	++
➢ Diagnosis by core biopsy	3a	C	++
➢ Diagnosis by FNB	3a	C	- -
➢ Staging (CT thorax & abd.; angiosarcoma: MRI brain)	4	D	++
➢ Prognostic factors: size, grade, margins	3a	C	++

*Therapy in specialized centres recommended

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Further Information

References

Guidelines Breast
Version 2017.1

Primary Angiosarcoma of the Breast* Therapy

	Oxford / AGO LOE / GR		
➢ **Surgery with wide clear margins, mostly as mastectomy**	3a	C	++
➢ **Breast-conserving therapy**	3a	C	-
➢ **SNB or axillary dissection if cN0**	3a	C	- -
➢ **Adjuvant chemotherapy (anthracycline/taxane-based)**	4	C	+/-
➢ **Adjuvant radiotherapy if high risk (size > 5 cm, R1)**	4	C	+/-

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Further Information

References

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*** Therapy in specialized centres recommended**

Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- **Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years**

- **Clinical presentation**
  - **> 5 years after BCT or mastectomy with irradiation**
  - **usually intracutaneously or subcutaneously in the irradiation area with livid discoloration**
  - **multiple foci**
  - **most often in advanced stages (II - III)**
  - **metastases mostly pulmonary**
  - **lymph node metastasis possible**

- **Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma**

- **Survival after 5 years: 15%**

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Further Information

References

Secondary Angiosarcoma of the Breast Therapy

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE / GR		
➢ Secondary mastectomy	3a	C	++
➢ Adjuvant chemotherapy (anthracycline/taxane-based)	2b	B	+/-
➢ Adjuvant radiotherapy if high risk (size > 5 cm, R1)	2b	B	+/-
➢ Regional hyperthermia (to improve local control) plus chemotherapy and/or radiotherapy	2b	B	+/-

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Further Information

References

Angiosarcoma of the Breast
Treatment of Local Recurrence and Metastases

Guidelines Breast
Version 2017.1

	Oxford / AGO LOE	GR	
Treatment of Local Recurrence:			
➢ R0 resection	4	C	++
➢ Radiotherapy, chemotherapy after R1 resection	4	C	+/-
Distant Metastases / Unresectable Tumors:			
➢ Treatment like soft tissue sarcomas	4	C	++
➢ Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)	2b	B	+
➢ Antiangiogenic treatment (e.g. in angiosarcoma)	4	C	+/-

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Further Information

References

Guidelines Breast
Version 2017.1

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)

- **Rare, estimated annual incidence <1 per 100,000 women with implants (median age 54 years)**
- **Occurrence predominantly of textured implants**
- **5-year OAS 89%**
- **Interval for lymphoma diagnosis: 8 years (median)**
- **Clinical presentation**
  - **Effusion only (60%)**
  - **Mass only (17%)**
  - **Effusion and mass (20%)**
- **Histological: CD30 + / ALK-T cell lymphoma**
- **Reporting obligation as SAE according to § 3 MPSV to the BfArM**

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Further Information

References

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Diagnosis -

Guidelines Breast
Version 2017.1

Further Information

References

	Oxford / AGO LOE / GR		
➢ Sonography (for newly occurring seromas 1 year after implant placement, tumor mass)	5	D	++
➢ Breast MRI on confirmation of the diagnosis	5	D	++
➢ Nodal status, PET-CT, bone marrow biopsy	5	D	++
➢ Cytology of effusion (for newly occurring seromas 1 year after implant placement) with requisition ”r/o BIA-ALCL”	5	D	++
➢ Lymphoma diagnosis on resection specimen and histological staging (acc. to Clemens 2016)	5	D	++
➢ Documentation of the implant (manufacturer, size, filling, surface, batch number)	5	D	++

Guidelines Breast
Version 2017.1

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Treatment -

	Oxford / AGO LOE / GR		
➢ Implant removal and complete capsulectomy including tumor removal	3a	C	++
➢ Removal of suspicious lymph nodes, no routine sentinel-node biopsy, no axillary dissection	4	D	++
➢ Polychemotherapy (e.g., CHOP) when extracapsular tumor infiltration	4	D	+
➢ Radiation for unresectable tumors or R1	5	D	+/-
➢ Reconstruction after 1 year disease-free interval	5	D	+

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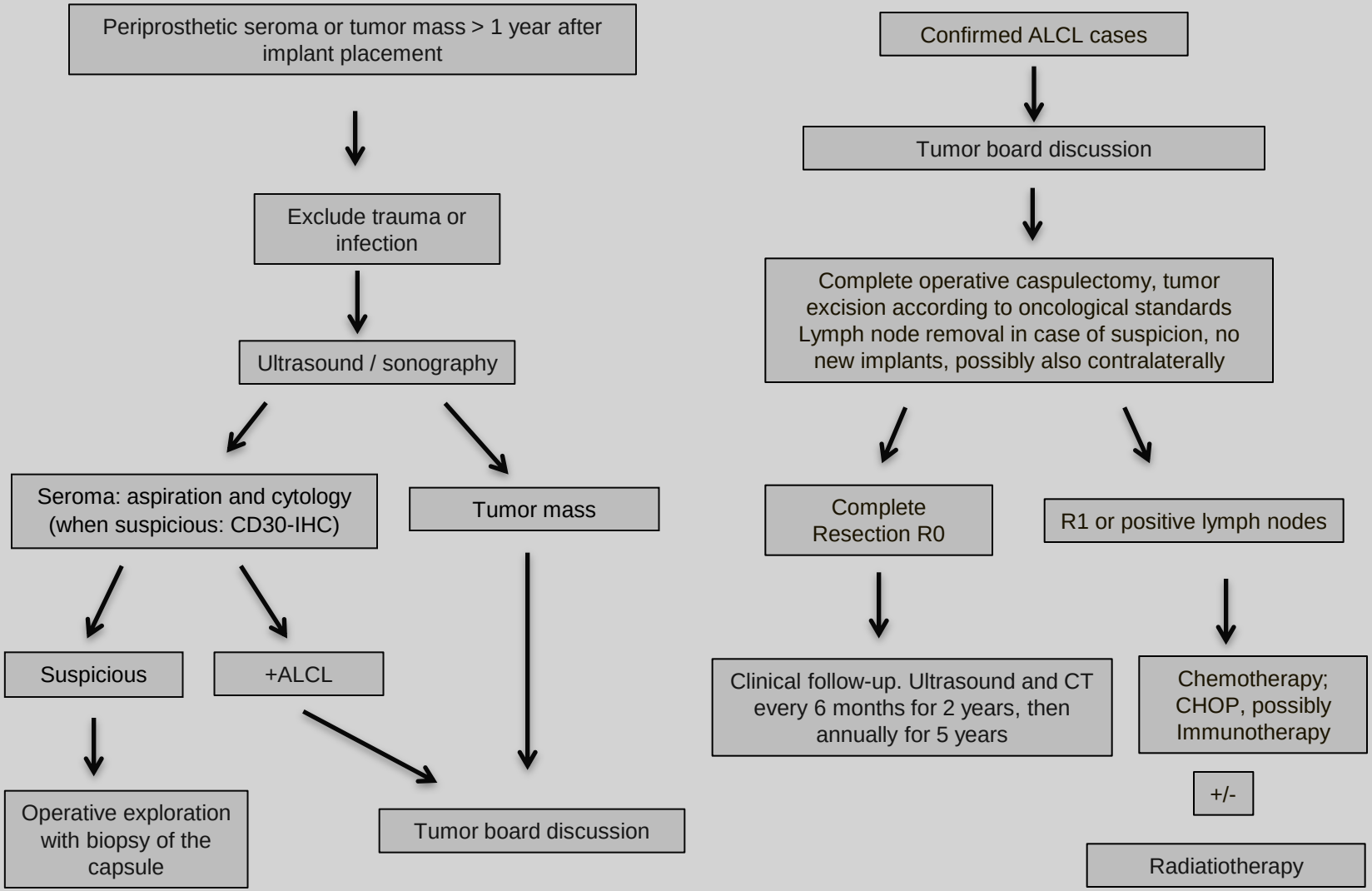
Further Information

References

Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Summary of the management (acc. to Noah 2017) -

Guidelines Breast
Version 2017.1



Breast Cancer: Specific Situations (2/38)

Further information:

Update January 2017 – Schütz / Sinn
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 (3/38)

No further information

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Breast Cancer in Young Women ≤ 35 years (4/38)

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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Breast Cancer During Pregnancy or Breast Feeding – Diagnosis and Surgery (5/38)

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 reluctancy 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, embryolethality, 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 on 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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2. Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, Fehm T, Van Calsteren K, Linn SC, Schlehe B, Gziri MM, Westenend PJ, Müller V, Heyns L, Rack B, Van Calster B, Harbeck N, Lenhard M, Halaska MJ, Kaufmann M, Nekljudova V, Amant F. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 Sep;13(9):887-96.
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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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3. Berry DL et al., Management of breast cancer during pregnancy using a standardized protocol J Clin Oncol 1999, 17: 855-861
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Reviews

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Breast Cancer During Pregnancy – Neo(adjuvant) Therapy(6/38)

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

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Statement: MTX (e.g. CMF

1. 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

1. Fanale MA et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. Clin Breast Cancer 2005, 6: 354-356 (Case Report)
2. Watson WJ. Herceptin (Trastuzumab) therapy during pregnancy: Association with reversible anhydramnios. Obstetrics and Gynecology 2005, 105: 642-643 (Case Report)
3. Loibl S. New Therapeutic Options for Breast Cancer during Pregnancy. Breast Care 2008; 3:171-176. (table overview of trastuzumab cases)

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8. Sarno MA et al. Are monoclonal antibodies a safe treatment for cancer during pregnancy? Immunotherapy 2013; 5(7):733-41.

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General information: Chemotherapy during pregnancy

1. Murthy RK, Theriault RL, Barnett CM, Hodge S, Ramirez MM, Milbourne A, Rimes SA, Hortobagyi GN, Valero V, Litton JK. Outcomes of children exposed in utero to chemotherapy for breast cancer. Breast Cancer Res. 2014 Dec 30;16(6):3414.

Breast cancer During Pregnancy – Delivery and Breast-Feeding (7/38)

Further information:

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

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3. Peccatori FA et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi160-70.
4. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, von Minckwitz G, Parokonnaya A, Stensheim H, Thomssen C, van Calsteren K, Poortmans P, Berveiller P, Markert UR, Amant F. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145-53.

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.

Breast Cancer and Pregnancy – Family Planning (8/38)

No further information

No references

Pregnancy Associated Breast Cancer: Outcome (9/38)

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 prosposed additional effects.

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Statement: Breast cancer during pregnancy / lactation: Outcome not compromized, if treated adaequately

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7. Amant F et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study J Clin Oncol. 2013;31(20):2532-9.
8. Litton JK et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. Oncologist. 2013;18(4):369-76.

Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

1. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19: 1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).
2. Kroman N et al. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. Acta Oncol. 2008;47(4):545-9
3. Azim HA Jr et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol 2013;31:73-79.

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Kroman N, et al. Prognostic influence of pregnancy before, around, and after diagnosis of breast cancer. Breast. 2003 Dec;12(6):516-21.

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3. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer. 2011 Jan;47(1):74-83. Epub 2010 Oct 11. Review.
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Geriatric Assessment (10/38)

Further information:

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

References:

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3. Lee et al. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006 295:801-08.
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Treatment for Fit Elderly Patients (11/38)

Further information:

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

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

References:

1. Dietz JR, Partridge AH, Gemignani ML, Javid SH, Kuerer HM. Breast Cancer Management Updates: Young and Older, Pregnant, or Male. Ann Surg Oncol. 2015 Oct;22(10):3219-24.

Statement: Treatment according to standard

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Statement: Surgery similar to „younger“ age

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Statement: Endocrine treatment (endocrine resp.)

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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 disesase 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 omittted when endocrine treatment with tamoxifen is planned.

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3. Giordano SH Radiotherapy in older women with low-risk breast cancer: why did practice not change? 2012 J Clin Oncol 30 (14): 1577-1578

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Statement: Trastuzumab

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Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (12/38)

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):

1. Hind D: Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006 Jan 25;(1):CD004272.

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Statement: No axillary clearing (≥ 60 y, cN0, ER+)

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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, ER+)

1. Hannoun-Levi JM, et al. Breast cancer in elderly women: is partial breast irradiation a good alternative? Breast Cancer Res Treat. 2003 Oct;81(3):243-51
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3. Kunkler I, et al. Postoperative breast irradiation: new trials needed in older patients. J Clin Oncol. 2003 May 1;21(9):1893; author reply 1893-4
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Statement: Hypofractionated radiotherapy

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.
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4. Ortholan C, et al. Long-term results of adjuvant hypofractionated radiotherapy for breast cancer in elderly patients. Int J Radiat Oncol Biol Phys. 2005 Jan 1;61(1):154-62.
5. Kirova YM, Campana F, Savignoni A, Laki F, Muresan M, Dendale R, Bollet MA, Salmon RJ, Fourquet A; for the Institut Curie Breast Cancer Study Group Breast-Conserving Treatment in the Elderly: Long-Term Results of Adjuvant Hypofractionated and Normofractionated Radiotherapy.Int J Radiat Oncol Biol Phys. 2009 Jan 2

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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3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 371;2008:1687-717

Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (13/38)

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 maligne breast tumors are not detected by mammography or they are coverd 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 of 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 with in 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.

References:

International registry:

1. Cardoso F, Bartlett J, Slaets L, van Deurzen C, van Leewen-Stok E, Porter P, Linderholm B, Hedenfalk I, Schroder C, Martens J, Bayani J, van Asperen C, Murray M, Hudis C, Middleton L, Vermeij J, Peeters S, Fraser J, Nowaczyk M, Rubio I, Aebi S, Kelly C, Ruddy K, Winer E, Nilsson C, Dal Lago L, Korde L, Benstead K, Van Den Weyngaert D, Bogler O, Goulioti T, Dif N, Messina C, Tryfonidis K, Bogaerts J, Giordano S. Characterization of male breast cancer: First results of the EORTC10085/TBCRC/BIG/NABCG International Male BC Program. SABCS 2014 (S6-05).

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
4. Dietz JR, Partridge AH, Gemignani ML, Javid SH, Kuerer HM. Breast Cancer Management Updates: Young and Older, Pregnant, or Male. Ann Surg Oncol. 2015 Oct;22(10):3219-24.
5. Deb S, Lakhani SR, Ottini L, Fox SB. The cancer genetics and pathology of male breast cancer. Histopathology. 2016 Jan;68(1):110-8.

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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4. Fogh S et al. Therapy for Male Breast Cancer: Functional Advantages With Comparable Outcomes Using Breast Conservation. Clin Breast Cancer. 2013;13(5):344-9.
5. Fields EC et al. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. J Radiat Oncol Biol Phys 2013;87(4):747-52
6. Cloyd et al. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983-2009. Ann Surg Oncol. 2013;20:1545–50
7. Zaenger D, Rabatic BM, Dasher B, Mourad WF. Is Breast Conserving Therapy a Safe Modality for Early-Stage Male Breast Cancer? Clin Breast Cancer. 2015 Nov 17. pii: S1526-8209(15)00278-5.

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

2. Flynn LW et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg. 2008 Apr;206(4):616-21
3. Boughey JC: Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. J Am Coll Surg. 2006 Oct;203(4):475-80. Epub 2006 Aug 23
4. De Cicco C: Sentinel node biopsy in male breast cancer. Nucl Med Commun 2004; 25: 139-143
5. Albo D et al. Evaluation of of lymph node status in male breast cancer patients: a role for sentinel lymph node biopsy. Breast Cancer Res Treat 2003 77:9-14

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
4. Thorlacius S, Sigurdson S, Bjanadottir H, et al. Study of a single BRCA2 mutation with high carrier frequency in a small population. Am J Hum Genet 1997; 60: 1079-1084

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
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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
5. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet. 2006 Feb 18;367(9510):595-604. Review. Erratum in: Lancet. 2006 Jun 3;367(9525):1818
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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 (14/38)

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 survial 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 fort he 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

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Benefit from Trimodal Treatment in Inflammatory Cancer (15/38)

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.

Inflammatory Breast Cancer (IBC; cT4d) (16/38)

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 ≥ 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].

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

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

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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

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Statement: in HER2 positive disease addition of trastuzumab and pertuzumab

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Statement :Sentinel lymph node

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Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary (CUP-Ax) (17/38)

Further information:

The incidence of axillary metastasis in carcinoma of unknown primary (CUP-Ax) is < 1% of all cases with axillary nodal metastasis (Pentheroudakis, 2010. In the great majority of cases the metastasis is due to a primary breast cancer, and only rarely secondary to another malignancy (Lanitis, 2009). Pathologically, about half of the cases are positive for estrogen receptors, and one third is HER2-positive (Montagna, 2011). Outcome is similar or better, compared to breast cancer with similar biology and stage (Sohn, 2014).

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Outcome

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Axillary Metastasis in Occult Breast Cancer(CUP-Ax) - Imaging Diagnostics- (18/38)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in < or = 75% of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management (Fehm 2013, Ko 2007). MRI is considered reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour (Lalonde 2005). Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial (Varadhachary 2004). All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinanalysis, fecal occult blood test (Jerusalem 2006).

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Statement: PET

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Further information and references:

Immunohistochemistry

Pathology workup of axillary metastasis in carcinoma of unknown primary is directed at excluding primaries other than breast cancer and identifying the molecular phenotype of the tumour metastasis. Because of the overwhelming probability of a primary breast cancer, it is recommended use routine IHC (ER, PgR, HER2, Ki67) markers, which are commonly used for the characterization of primary breast cancer (Montagna 2011). This should be supplemented by GATA3, a marker that is positive in most breast cancers, especially hormone-receptor positive tumor type, but has been reported to be positive also in 69% of ER-negative breast cancer (Ordonez 2013). In case of a triple-negative phenotype, other markers, such as SOX10, TTF1, and others are useful (Cimino-Mathews 2013, Provenzano 2015). This may be difficult in the individual patient (Wang 2013). Only rarely, a more generic approach may be necessary to characterize the disease (Wittekind 2008, Oien 2009)

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Gene expression profiling and other molecular approaches in CUP disease

The use of gene expression profiling for characterizing CUP disease has described using various codesets (Bender 2009, Monzon 2010, Tothill 2015, Varadhachary 2008). However most studies are lacking independent verification, and may not be accurate in defining the tissue of origin (Ades 2013, Greco 2010). However, more recently epigenetic profiling has been described as an alternative method to gene expression profiling (Moran 2016), and also genomic profiling may be useful in CUP disease to characterize the tumor for possible targeted therapy (Ross 2015).

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Axillary Metastasis in Occult Breast Cancer (CUP-Ax) - Treatment - (20/38)

Further information:

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 (Pentheroudakis 2010). However, the surgical treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal 2005) Probably these patients need to be treated as typical stage II patients. (Matsuoka 2003, Pavlidis 2003). 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. This is emphasized by current treatment guidelines (NICE 2010, ESMO 2011, DGHO 2014). If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed (Buqat 2002). Radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unkown primary (CUP) with inconspecious 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 obsereved. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% ($p<0,001$) (Barton 2011), and a trend towards reduced ipsilateral breast tumour recurrence in patients who received radiotherapy was observed in another study (Masinghe 2011).

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Statement: Axillary dissection

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Statement: Mastectomy without (in-)breast tumor:
LoE: 4; References 1-4 (retrospective analysis , case reports)

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Statement: Breast irradiation if breast MRI is negative

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Statement: Systemic treatment according N+ tumor

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2. Pentheroudakis, G., Lazaridis, G., & Pavlidis, N. (2010). Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Research and Treatment, 119(1), 1–11. http://doi.org/10.1007/s10549-009-0554-3

Paget´s Disease of the Breast (21/38)

Further information:

Pagest´s disease of the nipple is an uncommon presentation of invasive or non invasive carcinoma, or, more rarely, occurs without any underlying neoplasia. Clinically an eczematoid, erythematous weeping or crusted lesion with irregular borders is usually present. Nipple discharge and ulceration may occur, and an associated breast tumour may be palpable. Following the histologic confirmation of Pagest´s disease, the underlying malignancy of the breast should be sought for and treated accordingly. Pagest´s disease and the associated breast cancer usually is a HER2-positive disease.

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Paget´s Disease of the Breast - Diagnosis (22/38)

No further information

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Paget´s Disease of the Breast - Therapy (23/38)

No further information

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Statement: Sentinel-node excision (SNE)

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Borderline and Malignant Phyllodes Tumor (24/38)

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 2006, Chaney 2000). 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 2006).

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Borderline and Malignant Phyllodes Tumor – Diagnosis (25/38)

No further information

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Imaging

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Borderline and Malignant Phyllodes Tumor – Surgery (26/38)

Further information and references:

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 2006, Fou 2006, Cheng 2006). Some authors have seen an improved survival after Mastectomy (Ben Hassouna 2006). An axillary lymph node dissection generally is not indicated (Mishra 2013).

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

The mainstay of phyllodes tumour management has traditionally consisted of surgical excision with wide tumour-free margins, generally defined by some authors as at least 10 mm (Guillot 2011). However, more recent data suggest that narrow margins are usually sufficient with phyllodes tumours (Onkendi 2014, Lin 2013, Yom 2015, Mituś 2014).

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

Metastasis in malignant phyllodes occurs almost exclusively by hematogenous dissemination. Lymph node metastasis is very uncommon, and has been quoted as 0.6% (for malignant PT) the SEER Data base (Kim 2017), while the rate of lymph node enlargement in about 10% (Mishra 2013). Therefore, routine axillary clearance or sentinel node biosy is not recommended (Chen 2005, Mishra 2013).

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Statement: Staging (LoE 5 D, AGO+)

In malignant phyllodes tumours, the risk of developing of metastases has been described between 10% and 35%, mean 17%, as compared to 0.1% for benign and 1.6% for borderline PT (Tan 2016). Metastasis occurs mainly in lung and bone. With large series (Belkacemi 2008) distant metastasis was 3.4% for phylloides for tumors of any grading. Therefore, patients with benign or borderline phyllodes tumours do not need extensive tumor staging, while patients with malignant phyllodes tumours a much higher rate of distant recurrences was observed. In summary, as in breast cancer, clinical staging may be worthwhile, but an additional impact of regular imaging including PET and MRI in the follow-up has not been shown.

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Statements: Systemic adjuvant therapy/ Chemotherapy (LoE: 4) and Endocrine therapy (LoE: 5)

The treatment of local recurrent disease remains unsuccessful in most malignant phyllodes tumor patients. (Soumarova 2004). Surgery for locally recurrent tumours should aim to achieve adequate surgical margins (Tan 2006). The role of chemotherapy and hormonal manipulation in both the adjuvant and palliative settings remain to be defined (Chaney 2000, Chen 2005, Morales-Vásquez 2007, Spitaleri 2013).

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Statement: Adjuvant radiotherapy, if T ≥2cm (BCT) or T ≥10cm (mastectomy)

There is conflicting evidence for the benefit of radiotherapy in phylloides tumors, but it appears to be useful to decrease local recurrence rates in the high risk setting (Gnerlich 2014, Barth 2009, Belkacémi 2009, Mituś 2014). However, there is evidence that radiotherapy may actually improve survival for malignant phyllodes tumors (Kim 2017).

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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

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Borderline and Malignant Phyllodes Tumor – Adjuvant Therapy (27/38)

No further information

No references

Sarcomas of the Breast (28/38)

No further information

No references

Primary Angiosarcoma of the Breast (29/38)

Further information:

Angiosarcoma of the breast is the most common form of non-epithelial breast malignancy. *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. Both forms of angiosarcoma do not only differ regarding their mode of presentation, but also regarding molecular pathology, being often associated with MYC and FLT4 gene amplification. While the pathogenesis of primary angiosarcoma is unknown, the pathogenesis of secondary angiosarcoma is believed to be related to irreversible DNA damage induced by radiation, resulting in genome instability and by direct tumor induction by radiation through mutations of relevant cancer-related genes. 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.

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Primary Angiosarcoma of the Breast – Diagnosis (30/38)

Further information:

Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm (**Scow: 7 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.

The grading for angiosarcoma of the breast is performed according to Rosen (1988). However, the prognostic significance of this grading system is controversial (Nascimento 2008).

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Primary Angiosarcoma of the Breast – Therapy (31/38)

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 mostly large tumor sizes both in primary and in secondary angiosarcoma, simple mastectomy remains the treatment of choice. The frequency of lymph node metastasis is < 1%. Therefore, routine sentinel node biopsy is not indicated. 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 anthracylines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

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Adjuvant Treatment (Chemotherapy, Radiotherapy)

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Secondary Angiosarcoma of the Breast (32/38)

Further information:

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 symdrome and is not radiotherapy-associated and therefore not considered here. The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation.

The role of adjuvant radiotherapy and chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with antracycline-ifosfamide or gentcitabine-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. Thererfore, the role of adjuvant chemotherapy for AS of the breast remains unclear.

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Secondary Angiosarcoma of the Breast – Therapy (33/38)

No further information

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Angiosarcoma of the Breast – Treatment of Local Recurrence and Metastases (34/38)

No further inforamtion

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Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) (35/38)

Further information :
(adapted from Frequently Asked Questions (FAQ): A Guide to Breast Implant-Associated Anaplastic Large Cell Lymphoma http://www.thepsf.org/Documents/Clinical/PROFILE/profile-faq.pdf)

Breast implant-associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a rare cancer that that can develop around breast implants In the US, the FDA reported in 2016 that 258 BIA-ALCL adverse events. BIA-ALCL occurs at a mean of eight years following implantation. Histologically, it can be characterized as a CD30+/ALK- T-cell lymphoma most commonly. The estimated incidence is less than 1 per 100,000 implants per year. The recommendation is that surgeons should consider including BIA-ALCL in breast implant informed consents. Presenting symptoms include spontaneous seroma or effusion after one year from implantation. Although common causes of a delayed seroma are infection or trauma, suspicious effusions should receive a fine needle aspiration sent for pathologic review. Routine screening or prophylactic implant removal for asymptomatic patients is not recommended.

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Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Diagnosis 36/38)

Further information:

(adapted from Frequently Asked Questions (FAQ): A Guide to Breast Implant-Associated Anaplastic Large Cell Lymphoma http://www.thepsf.org/Documents/Clinical/PROFILE/profile-faq.pdf)

For suspicious cases, patients should receive an ultrasound evaluation to confirm the presence and extent of an effusion, determine if there is presence of a mass, and evaluate regional lymph node basins for lymphadenopathy. Fine needle aspiration is performed of an effusion, which is sent to an experienced hematopathologist for culture, flow cytometry, and cytology. It is critical to include a clinical history and to direct the pathologist to "rule out BIA-ALCL" as well as to perform CD30 surface protein immunohistochemistry. Ultrasound is an acceptable screening tool for the two-thirds of patients presenting with an effusion or the one-third with a mass. PET/CT and MRI are reserved for confirmed cases and there does not appear to be a role for mammography. Physicians are strongly encouraged to include a lymphoma oncologist for medical management and future disease surveillance. Preoperative evaluation includes a bone marrow biopsy to distinguish from other systemic forms of ALCL, which have a more aggressive clinical course and poor prognosis. Patients should also receive a preoperative PET/CT scan to evaluate for baseline extent of disease, masses, and involved lymph nodes.

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Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) –Treatment (37/38)

Further information:

(adapted from Frequently Asked Questions (FAQ): A Guide to Breast Implant-Associated Anaplastic Large Cell Lymphoma http://www.thepsf.org/Documents/Clinical/PROFILE/profile-faq.pdf)

In confirmed cases of BIA-ALCL definitive treatment for most patients is removal of the implants and total capsulectomy, which includes complete resection of any mass associated with the capsule. Physicians should consider possible removal of contralateral breast implants with capsulectomy as several bilateral cases have been detected incidentally. The implant, capsule, and effusion should all be sent to pathology for evaluation. Suspicious lymph nodes should also be excised. At this time, there does not appear to be a role for routine sentinel lymph node biopsy or for full axillary dissection if no clinically positive nodes are present. Surgeons are strongly encouraged to include a surgical oncologist for resection of disease as well as resection of involved lymph nodes. Surgery should be performed with strict oncologic technique including use of specimen orientation sutures and placement of surgical clips within the tumor bed. Complete surgical resection may be sufficient treatment for the majority of patients. The role for further adjunctive therapy such as chemotherapy (CHOP regimen: cyclophosphamide, doxorubicin, vincristine, prednisolone), clinical trials of targeted immunotherapy (Brentuximab vedotin), and chest wall radiation therapy for unresectable tumors or positive margins is the subject of ongoing research.

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Breast-Implant Associated Anaplastic Large-Cell lymphoma (BIA-ALCL) –Summary of the Management (38/38)

No further information

No references

Guidelines Breast
Version 2017.1

Breast Cancer
Follow-Up

START

Guidelines Breast
Version 2017.1

Breast Cancer
Follow-Up

- **Versions 2002–2016:**
  Bauerfeind / Bischoff / Blohmer / Böhme / Costa / Diel / Gerber / Hanf / Heinrich / Huober / Janni / Kaufmann / Kümmel / Lux / Maass / Möbus / Mundhenke / Oberhoff / Rody / Scharl / Solomayer / Thomssen

- **Version 2017:**
  Maass / Friedrich

Breast Cancer Follow-Up Objectives

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE / GR
Early detection of curable events	
➢ In-breast recurrence	1a B ++
➢ Loco-regional recurrence*	1a B ++
Early detection of metastases	
➢ Early detection of symptomatic metastases	3b C +
➢ Early detection of asymptomatic metastases	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**

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Breast Cancer Follow-Up Objectives

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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

	Oxford / AGO LoE / GR
➢ **Re-evaluation of current adjuvant therapy**	**5 D ++**
➢ **incl. monitoring of compliance with endocrine therapies**	
➢ **Pro-active improvement of compliance:**	**5 D ++**
➢ **Patient information about efficacy data of 5-10 year endocrine therapy**	
➢ **Early therapy of side effects (sports, NSAIDs, vitamin D / calcium)**	

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Breast Cancer Follow-Up Objectives

Guidelines Breast
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	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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Version 2017.1

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)	5	D	++
➢ **Weight intervention** (if BMI <18.5 and >40)	2a	B	+
➢ **Reduction of dietary intake** (at least 15 % calories from fat) in HR neg. breast cancer patients is associated with improved overall survival	2b	B	+
➢ **Avoid Smoking** (bc related mortality 2 x and BC unrelated mortality 4 x elevated)	2b	B	++
➢ **Reduce alcohol consumption below 6 g/d**	2b	B	+
➢ **Moderate sport intervention when physical activity was reduced before**	1b	A	++

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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**

Routine Follow-Up Examinations in Asymptomatic Patients

Tests:	Oxford / AGO LoE	GR	
➢ History (specific symptoms)	1a	A	++
➢ Physical examination	1a	B	++
➢ Breast self-examination	5	D	+
➢ Mammography	1a	A	++
➢ Sonography of the breast	2a	B	++
➢ Routine MRI of the breast	3a	B	+/-
➢ MRI of the breast in case of inconclusive conventional imaging	3b	B	+
➢ Pelvic examination	5	D	++
➢ DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI	5	D	+

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Routine Follow-Up Examinations in Asymptomatic Patients

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	Oxford / AGO LoE / GR		
➢ Routine biochemistry (incl. tumor markers)	1a	A	-
➢ Ultrasound of the liver	1a	A	-
➢ Bone scan	1a	A	-
➢ Chest X-ray	1a	A	-
➢ CT of chest, abdomen and pelvis	2a	D	-
➢ Detection of isolated / circulating tumor cells	2a	D	-
➢ PET	2b	B	-
➢ Whole body MRI	2b	B	-

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Early Detection of Potentially Curable Events

	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	A	++
➢ Magnetic resonance imaging (MRI)	3a	B	+/-

Early Detection of Potentially Curable Events

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE		
Contralateral breast cancer:			
➢ Rel. risk: 2,5–5			
➢ Incidence: 0,5–1,0 % / year			
➢ **Breast self-examination**	5	D	+
➢ **Physical examination, mammography & US**	1a	A	++
➢ **Routine breast MRI**	5	D	-

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Early Detection of Potentially Curable Events

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	Oxford / AGO LoE / GR		
Unrelated site carcinoma:			
➢ Colon RR 3,0; endometrium RR 1,6 ovary RR 1,5; lymphoma RR 7			
➢ Screening for secondary malignancies according to current guidelines	5	D	++
➢ Pelvic examination and PAP smear	5	D	++
➢ Routine endometrial ultrasound / biopsy	1b	B	-

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Follow-Up Care for Breast Cancer

Recommendations for asymptomatic pts.
(modified ASCO-ACS guidelines 2016, NCCN 2.2016 guidelines and S3 national German guideline 2012)

Clinical follow-up		Follow-Up*		Screening
Years after primary therapy		1 2 3	4 5	> 5
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 additionally 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

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Breast Cancer Follow-up
Duration and Breast Nurses

Guidelines Breast
Version 2017.1

	Oxford / LoE	/ GR	AGO
➢ **Duration of follow-up**			
➢ **until 5 yrs**	1c	A	++
➢ **until 10 yrs**	1c	A	+
➢ **Surveillance by specialized breast nurses**	2b	B	+/-*

*Studies recommended

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Version 2017.1

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.**

Ribelles et al. BCR 2013

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)

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Statement: sexual disorders and cognitive impairment:

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

No further information

References:

Statement: Re-evaluation of current adjuvant therapy

Expert opinion Organkommission

Statement: Monitoring of compliance

1. Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, Gelmon K, Whelan T, Strasser-Weippl K, Rubin S, Sturtz K, Wolff AC, Winer E, Hudis C, Stopeck A, Beck JT, Kaur JS, Whelan K, Tu D, Parulekar WR. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med. 2016 Jul 21;375(3):209-19.
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Statement: Early Detection of Distant Disease

1. Rojas, MP et al: Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005 Jan 25;(1) Review. Update in: Cochrane Database Syst Rev 2016; (5) CD001768
2. Khatcheressian JL, Hurley P, Bantug E, et al.: Breast Cancer Follow-up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update . J Clin Oncol. 2013 March 1; 31(7):961-965.
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7. The GIVIO Investigators: Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 1994; 271: 1587–1592

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

No further information

References:

Statement: Early Detection

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Statement: Psycho-social aspects

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6. Davies JE, French MA, Allen T: Follow-up for a fearful patient. Adv Nurse Pract 2001; 9(2): 22
7. Maunsell E, Brisson J, Deschenes L: Social support and survival among women with breast cancer. Cancer 1995; 76(4): 631-7

Statement: prophylactic surgery

1. Rhiem K, Engel C, Graeser M, Zachariae S, Kast K, Kiechle M, Ditsch N, Janni W, Mundhenke C, Golatta M, Varga D, Preisler-Adams S, Heinrich T, Bick U, Gadzicki D, Briest S, Meindl A, Schmutzler RK: The risk of contralateral breast cancer in patients from BRCA ½ negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: a retrospective cohort study. Breast Cancer Res. 2012; 14(6): R156. doi: 10.1186/bcr3369.

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

No further information

References:

Statement: Early Detection

1. Khatcheressian JL, Hurley P, Bantug E, et al.: Breast Cancer Follow-up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update . J Clin Oncol. 2013 March 1; 31(7):961-965.
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Statement: Psycho-social aspects

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6. Maunsell E, Brisson J, Deschenes L: Social support and survival among women with breast cancer. Cancer 1995; 76(4): 631-7

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

Weight intervention

Chajès V, Romieu I.: Nutrition and breast cancer. Maturitas, 2014; 77 (1): 7–11

Moderate sport intervention when physical activity was reduced

Chlebowski RT. Nutrition and physical activity influence on breast cancer incidence and outcome. Breast 2013; Aug;22 Suppl 2: S30-7

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

No further information

References:

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

No further information

References:

Statement: History (specific symptoms)

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4. Parmeshwar R, Margenthaler JA, Allam E, et al.: Patient Surveillance After Initial Breast cancer Therapy Variation by Physician Specialty. Am J Surg 2013; 206(2): 218-222.
5. Margenthaler JA, Allan E, Cheng L, et al.: Surveillance of Patients With Breast Cancer After Curative-Intent Primary Treatment: Current Practice Patterns. Journal of Oncology Practice 2012; 8(2): 79 – 83.

Statement: Physical examination

1. Khatcheressian JL, Hurley P, Bantug E, et al.: Breast Cancer Follow-up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update . J Clin Oncol. 2013 March 1; 31(7):961-965.
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4. Margenthaler JA, Allan E, Cheng L, et al.: Surveillance of Patients With Breast Cancer After Curative-Intent Primary Treatment: Current Practice Patterns. Journal of Oncology Practice 2012; 8(2): 79 – 83.

Statement: Breast self-examination

Expert Opinion

Statement: Mammography

1. Khatcheressian JL, Hurley P, Bantug E, et al.: Breast Cancer Follow-up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update . J Clin Oncol. 2013 March 1; 31(7):961-965
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Statement: Sonography of the breast

1. Jung Hyun-Yun., Min Jung Kim, Eun-Kyung Kim, et al.: Imaging Surveillance of Patients with Breast Cancer after Primary Treatment: Current Recommendations. Korean J Radiol 2015;16(2):219-228
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4. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, Mallek R, Sickles EA: Follow-up of palpable circumscribed noncalcified solid breast masses at mammography and US: can biopsy be averted? Radiology 2004; 233(3): 850-6. Epub 2004 Oct 14.

Statement: MRI of the breast in case of inconclusive conventional imaging

1. Shah C, Ahlawat S, Khan A, Tendulkar RD, Wazer DE, Shah SS, Vicini F. The Role of MRI in the Follow-up of Women Undergoing Breast-conserving Therapy. Am J Clin Oncol. 2016 Jun;39(3):314-9.
2. Lehman CD, Lee JM, DeMartini WB, Hippe DS, Rendi MH, Kalish G, Porter P, Gralow J, Partridge SC. Screening MRI in Women With a Personal History of Breast Cancer. J Natl Cancer Inst. 2016 Jan 7;108(3).
3. Warner E: The role of magnetic resonance imaging in screening women at high risk of breast cancer. Top Magn Reson Imaging. 2008; 19(3):163-9. Review.
4. DeMartini W, Lehman C: A review of current evidence-based clinical applications for breast magnetic resonance imaging. Top Magn Reson Imaging 2008;19(3):143-50. Review.

Statement: Pelvic examination

Expert Opinion

1. Khatcheressian JL, Hurley P, Bantug E, et al.: Breast Cancer Follow-up and Management After Primary Treatment: American Society of Clinical Oncology Clinical Practice Guideline Update . J Clin Oncol. 2013 March 1; 31(7):961-965
2. Geurts SM1, de Vegt F, Siesling S, Flobbe K, Aben KK, van der Heiden-van der Loo M, Verbeek AL, van Dijck JA, Tjan-Heijnen VC: Pettern of follow up care and early relapse detection in breast cancer patients. Breast Cancer Res Treat 2012; 136(3): 859-68
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Statement: Dexa scan

Expert Opinion

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

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

No further information

References:

Statement: Magnetic resonance imaging (MRI) of the breast

1. Shah C, Ahlawat S, Khan A, Tendulkar RD, Wazer DE, Shah SS, Vicini F: The Role of MRI in the Follow-up of Women Undergoing Breast-conserving Therapy. Am J Clin Oncol. 2016 Jun;39(3):314-9. doi: 10.1097/COC.0000000000000290
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Statement: Routine biochemistry (incl. tumor markers)

1. Harris L, et al.: Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-stage Invasive Breast Cancer: American Society of Clinical Practice Guideline. J Clin Oncol 2016; 34(10): 1134-50
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Statement: Ultrasound of the liver

1. Rojas, MP et al: Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005 Jan 25;(1) Review. Update in: Cochrane Database Syst Rev 2016; (5) CD001768
2. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol. 2003; 30(3): 338-48. Review.
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5. The GIVIO Investigators: Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. JAMA 1994; 271: 1587–159

Statement: Bone scan

1. Rojas, MP et al: Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005 Jan 25;(1) Review. Update in: Cochrane Database Syst Rev 2016; (5) CD001768
2. Emens LA, Davidson NE. The follow-up of breast cancer. Semin Oncol 2003; 30(3): 338-48. Review
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4. RDel Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V (for the National Research Council Project on Breast Cancer Follow-up): Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. JAMA 1994; 271: 1593–1597
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Statement: Chest X-ray

1. Rojas, MP et al: Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005 Jan 25;(1) Review. Update in: Cochrane Database Syst Rev 2016; (5) CD001768
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Statement: CT of chest, abdomen and pelvis

1. Rojas, MP et al: Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev 2005 Jan 25;(1) Review. Update in: Cochrane Database Syst Rev 2016; (5) CD001768
2. Emens LA, Davidson NE: The follow-up of breast cancer. Semin Oncol 2003; 30(3): 338-48. Review.
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Statement: Detection of isolated/circulating tumor cells

1. Janni W, Vogl FD, Wiedswang G, Synnestvedt M, Fehm T, Jückstock J, Borgen E, Rack B, Braun S, Sommer H, Solomayer EF, Pantel K, Nesland JM, Friese K, Naume B: Persistence of disseminated tumor cells (DTC) in bone marrow (BM) during Follow-up predicts increased risk for relapse – Up-date of the pooled European data. Clin Cancer Res 2011; 17(9): 2967-76
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Statement: PET

1. Lei L, Wang X, Chen Z. PET/CT Imaging for Monitoring Recurrence and Evaluating Response to Treatment in Breast Cancer. Adv Clin Exp Med. 2016 Mar-Apr;25(2):377-82.
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5. Moon DH, Maddahi J, Silverman DH, Glaspy JA, Phelps ME, Hoh CK: Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 1998; 39(3): 431-5

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; 43(3): 325-9
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Early Detection of Potentially Curable Events (11/16)

No further information

References:

Statement incidence

1. Wapnir IL, Anderson SJ, Mamounas EP et al.: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 2006; 24:2028-2037
2. Perry NM: Quality assurance in the diagnosis of breast disease. EUSOMA Working Party. Eur J Cancer 2001; 37: 159-172

Statement breast self examination

1. 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; 97(12): 1632-41
2. Khatcheressian JL, Wolff AC, Smith TJ: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol. 2006 Nov 1;24(31):5091-7
3. Thomas DB, Gao DL, Ray RM et al.: Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst 2002; 94(19): 1445-57

Statement physical examination, mammography & US

1. Tsai WC, Wei HK, Hung CF, Kwang-Jane Lin C, Hung-Chun Cheng S, Chen CM, Wang YA. Better Overall Survival for Breast Cancer Patients by Adding Breast Ultrasound to Follow-Up Examinations for Early Detection of Locoregional Recurrence-A Survival Impact Study. Ultrasound Med Biol. 2016 Sep;42(9):2058-64.
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6. 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 Cance. 2007; 97(12): 1632-41
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10. Samant R et al.: Diagnosis of metachronous contralateral breast cancer. Breast J 2001; 7:405-410

11. Mellink W et al.: The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. Cancer 1991; 67:1844-1848

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

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Statement: Risk according to intrinsic subtype

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Early Detection of Potentially Curable Events (13/16)

No further information

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Statement: Pelvic examination and PAP smear

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Statement: Endometrial ultrasound / biopsy

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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 and 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

START

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Loco-regional Recurrence

- **Version 2002:**
  Brunnert / Simon
- **Versions 2003–2016:**
  Audretsch / Bauerfeind / Budach / Costa / Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Hanf / Harbeck / Lisboa / Maass / Mundhenke / Rezai / Solomayer / Souchon / Thomssen / Wenz
- **Version 2017:**
  Bauerfeind / Thomssen

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Loco-regional Recurrence Incidence and Prognosis

Localization	Frequency (%)	5-y. Overall Survival (%)
Ipsilateral recurrence[1] (post BCT + irradiation)	**10 (2–20)**	**65 (45–79)**
Chest wall[1] (post mastectomy)	**4 (2–20)**	**50 (24–78)**
As above plus supraclavicular fossa[2]	**34%**	**49% (3-y. OS)**
Axilla:		
After **ALND[1]**	**1 (0.1–8)**	**55 (31–77)**
After **SNB[4]**	**1**	**93%**
Multiple localizations[2]	**16 (8–19)**	**21 (18–23)**

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

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Further Information

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Loco-regional Recurrence Staging

Examinations before treatment:

	Oxford LoE	AGO GR	
➢ Tissue biopsy	5	D	++
➢ Re-assessment of ER, PgR, HER2	3b	B	++
➢ Complete re-staging	5	D	++

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Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

Increased risk for loco-regional recurrence	Oxford LoE
➢ Young age	1a
➢ Positive microscopic margins (R1) of the primary tumor	1a
➢ Omitting adjuvant radiotherapy (if indicated)	1a
➢ Extensive intraductal component	1b
➢ Vessel invasion	1b
➢ HER2 positive and triple negative > Luminal B-like > luminal A-like	2a
➢ Number of involved lymph nodes	1a
➢ Grading (G3)	1b*
➢ Elevated proliferation markers: e.g. Ki67;	2b
➢ pT (> 2)	1b*
* node negative	1a
➢ Inflammatory breast cancer	2b
➢ Medial tumor localisation	4
➢ Obesity (Body mass index)	1a

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Further Information

References

Metaanalysis: TNBC and Local Recurrence

Wang et al, Surg Oncol. 2013 Dec;22(4):247-55.

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

Lowery AJ et al. 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.

***most pts. were treated in the time before routine adjuvant trastuzumab use**

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Loco-regional Recurrence
Prognostic / Predictive factors

	Oxford LoE	AGO GR	
Parameters of the locally recurrent tumor to define the risk for re-recurrence			
➢ Tumor size	2a	B	
➢ Multifocality	2a	B	
➢ Localisation	2b	B	
➢ Negative progesterone receptor	3b	B	
Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival			
➢ Early (<2-3 yrs.) vs. late recurrence	2b	B	
➢ LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
Predictive factors for treatment considerations			
➢ HER2	2b	B	++
➢ ER and PgR	2b	B	++

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Further Information

References

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

Panet-Raymond V et al., 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

	Oxford LoE	Oxford GR	AGO
➢ Mastectomy (aim: R0)	3b	B	++
➢ Re-BCS with tumor-free margins (R0)	3b	C	+/-
➢ Axillary intervention after prior AxDiss if cN0	4	C	-
➢ SLNE after prior SLNE if cN0*	1b	B	-
➢ Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial indication)	5	D	+

*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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	Oxford LoE	AGO GR	
➢ Curative situation: R0-resection	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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References

Loco-regional Recurrence after R0-Resection
Systemic Treatment

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According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)	**Oxford LoE**	**Oxford GR**	**AGO**
➢ **Endocrine therapy in endocrine responsive tumors**	**2b**	**B**	**++**
➢ **Chemotherapy (consider preoperative)**	**2b**	**B**	**+**
➢ **In case of HER2 positive disease, chemotherapy + HER2 targeted therapy**	**5**	**D**	**+**

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Further Information

References

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).

Aebi et al. Lancet Oncol 2014

Locoregional Recurrence in Case R0 Resection not Likely - Systemic Treatment

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	Oxford LoE	AGO GR	
According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)			
➢ **Endocrine therapy in endocrine responsive tumors**	2b	B	++
➢ **Chemotherapy (pre- or postoperatively)**	2b	B	++
➢ **HER2-targeted therapy in HER2-positive tumors (with chemotherapy)**	5	D	++

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References

Ipsilateral Recurrence after BCT Radiotherapy

	Oxford LoE	AGO	GR
After Re-BCS			
➢ Whole breast irradiation (in case adjuvant radiotherapy was not performed)	3b	C	++
➢ Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)	3b	C	+/-
After mastectomy			
➢ Radiation of chest wall +/- regional lymph nodes (14% involved supraclavicular metastases)	2b	B	+/-
➢ Radiation dose escalation (+10%)	3b	C	-
➢ Repeated irradiation (e.g. as brachytherapy) with hyperthermia	3a	C	+/-

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References

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy

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	Oxford LoE / GR	AGO	
Chest-Wall Recurrence after Mastectomy			
➢ If no prior postmastectomy radiotherapy			
➢ Curative situation: irradiation of the chest wall +/- regional lymph nodes	2b	B	+
➢ Re-irradiation (chest wall + hyperthermia)	1b	B	+/-
Axillary recurrence			
Irradiation of axilla after R0-surgery			
➢ No prior adjuvant irradiation of the axilla	3b	C	+
➢ Adjuvant irradiation of the axilla	5	D	+/-

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References

Loco-Regional Recurrence
Treatment Options in Non Curative Cases

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	Oxford / AGO LoE	GR	
➢ 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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Further Information

References

FORSCHEN
LEHREN
HEILEN

Loco-regional Recurrence (2/18)

Further information and references:

Screened data bases: Pubmed 2005 - 2017, ASCO 2005 – 2017, SABCS 2009 – 2017, Cochrane data base

Guidelines:

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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 lmyph node biopsy. The survival rate is higher than 90 % in these patients.

References:

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5. www.tumorregister-muenchen.de

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. Re-staging can be performed by conventional techniques, CT scans, MRI or Pet scans depending of practioners choice.

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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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Informative for the whole list of factors:

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Statement: Increased risk for loco-regional recurrence

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Statement: Young age

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<u>Statement: Positive microscopic margins</u>

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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

1. van der Hage JA, Mieog JS, van de Velde CJ, Putter H, Bartelink H, van de Vijver MJ Impact of established prognostic factors and molecular subtype in very young breast cancer patients:pooled analysis of four EORTC randomized controlled trials. Breast Cancer Res Breast Cancer Res 24;13(3):R68, 2011
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Statement: Grading G3

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Statement: pT > 2

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Statement: pN (N1 vs. N0)

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2. www.tumorregister-muenchen.de

Statement: pN (N1 vs. N0) and number of involved lymph nodes

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Statement: Medial tumor localisation

1. Knauerhase H, Strietzel M, Gerber B, Reimer T, Fietkau R. Tumor location, interval between surgery and radiotherapy and boost technique influence local control after breast conserving surgery and radiation: retrospective analysis of monoinstitutional long-term results. Int J Radiat Oncol Biol Phys 72: 1048-55, 2008

Statement: elevate proliferation marker, esp. Ki67

1. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28(10):1684-91, 2010

Statement: Inflammatory breast cancer

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

Statement: Nomograms

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Statement: Obesity

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Recent evidence for Multigene arrays predicting risk for local relapse:

1. Drukker CA[1], Elias SG, Nijenhuis MV, Wesseling J, Bartelink H, Elkhuizen P, Fowble B, Whitworth PW, Patel RR, de Snoo FA, van 't Veer LJ, Beitsch PD, Rutgers EJ. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
2. Erratum to: Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Drukker CA, Elias SG, Nijenhuis MV, Wesseling J, Bartelink H, Elkhuizen P, Fowble B, Whitworth PW, Patel RR, de Snoo FA, Van't Veer LJ, Beitsch PD, Rutgers EJ. Breast Cancer Res Treat. 2015 Jan 21.
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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

1. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006

Statement: Localisation

1. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. Int J Radiat Oncol Biol Phys 64(5):1401-9, 2006

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

Statement: ER-pos/PgR-pos vs ER-pos/PgR-neg or ER-neg/PgR-neg

1. Wapnir IL, Gelber S, Anderson SJ, Mamounas EP, Robidoux A, Martín M, Nortier JW, Geyer CE Jr, Paterson AH, Láng I, Price KN, Coates AS, Gelber RD, Rastogi P, Regan MM, Wolmark N, Aebi S; CALOR trial investigators. Poor Prognosis After Second Locoregional Recurrences in the CALOR Trial. Ann Surg Oncol. 2017 Feb;24(2):398-406

Statement: Early vs. Late recurrence

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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

1. Panet-Raymond V, Truong PT, Alexander C, Lesperance M, McDonald RE, Watson PH. Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. Cancer 117:2035, 2011
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
2. Haffty BG, Reiss M, Beinfield M, Fischer D, Ward B, McKhann C. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol 14: 52–57, 1996
3. Kuo SH, Huang CS, Kuo WH, Cheng AL, Chang KJ, Chia-Hsien Cheng J. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Oncology Biol Phys 72: 1456-64, 2008

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence (10/18)

No further information

No references

Ipsilateral Recurrence after BCT - Surgery (11/18)

Further information:

Mastectomy is the current standard of care for ipsilateral recurrence of breast carcinoma. Some retrospective analyses showed that second conservative treatments for local relapse were feasible and gave results comparable to standard mastectomy. A repeat BCT demands tumor-free margins and an interstitial brachytherapy. However, the indication for second lumpectomy is restricted for suited patients (small-size, low-risk). As data from prospective randomized clinical trials are missing, an impaired regional tumor control (without disadvantages for overall survival) cannot be ruled out completely. In patients with distant metastases a local surgery is indicated in pain, endangered ulceration and in some cases for psychological reasons. SLNB after previous axillary surgery is technically feasible after breast conserving therapy, but since randomized trials support the value of systemic therapy for all patients with invasive LR, reoperative SLNB, although feasible, may not be necessary.

References:

Statement: Mastectomy (aim: R0)

1. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomesof salvage mastectomy vs. salvage breast-conserving surgery and prognosticfactors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
2. Shin E, Suemasu K, Sonoo H, Taguchi T, Nishi T, Nishimura R, Haga S, Mise K,Kinoshita T, Murakami S, Yoshimoto M, Tsukuma H, Inaji H: Analysis of ipsilateral breast tumor recurrences after breast-conservingtreatment based on the classification of true recurrences and new primary tumors. Breast Cancer 12(2):104-11, 2005
3. Kolben T, Schwarz TM, Goess C, Blume C, Degenhardt T, Engel J, Wuerstlein R, Ditsch N, Harbeck N, Kahlert S Surgical management of ipsilateral breast tumor recurrence. Int J Surg. 2015 Nov;23(Pt A):141-6.
4. NCCN clinical practice Guidelines in oncology(NCCN guidelines) breast cancer Version 3.2015 NCCN.org

Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0

1. Intra M, TrifiròG, 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 AJ[1], 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 MS[1], 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 CC[1], 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 treatedwithout 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 treatedwithout 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

Chemo Therapy by Loco-regional Recurrence (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)
5. Kuo SH, Huang CS, Kuo WH, Cheng AL, Chang KJ, Chia-Hsien Cheng J. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17Version 3.2012
7. F. Cardoso ,A. Costa , E. Senkus , M. Aapro, F. Andre, C.H. Barrios , J. Bergh, G. Bhattacharyya , L. Biganzoli , M.J. Cardoso , L. Carey , D. Corneliussen-James , G. Curigliano , V. Dieras , N. El Saghir , A. Eniu , L. Fallowfield , D. Fenech , P. Francis , K. Gelmon , A. Gennari, N. Harbeck , C. Hudis , B. Kaufman, I. Krop , M. Mayer , H. Meijer , S. Mertz , S. Ohno , O. Pagani , E. Papadopoulos , F. Peccatori , F. Penault-Llorca , M.J. Piccart , J.Y. Pierga , H. Rugo , L. Shockney , G. Sledge , S. Swain , C. Thomssen , A. Tutt , D. Vorobiof , B. Xu , L. Norton , E. Winer. 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259

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: outcomesof salvage mastectomy vs. salvage breast-conserving surgery and prognosticfactors 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

Statement Re-Irradiation of the chest wall with hyperthermia:

1. Auoragh A, Strnad V, Ott OJ, Beckmann MW, Fietkau R. Re-irradiation of the chest wall for local breast cancer recurrence : Results of salvage brachytherapy with hyperthermia. Strahlenther Onkol. 2016 Sep;192(9):617-23.
2. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1073-87.

3. Oldenborg S, Valk C, van Os R, Oei B, Venselaar J, Vörding PZ, van Randen A, Crezee H, van Tienhoven G, Rasch C. Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016 Apr;192(4):240-7.

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. Auoragh A, Strnad V, Ott OJ, Beckmann MW, Fietkau R. Re-irradiation of the chest wall for local breast cancer recurrence : Results of salvage brachytherapy with hyperthermia. Strahlenther Onkol. 2016 Sep;192(9):617-23.
3. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1073-87.
4. Oldenborg S, Valk C, van Os R, Oei B, Venselaar J, Vörding PZ, van Randen A, Crezee H, van Tienhoven G, Rasch C. Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016 Apr;192(4):240-7.

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: Concomitant radio-chemotherapy

1. Mcormick 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. Mcormick 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. Oldenborg S, Van Os RM, Van rij CM, Crezee J, Van de Kamer JB, Rutgers EJ, Geijsen 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. Kouloulias 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. Kouloulias 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, Wiggenraad 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 breastcancer 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):713-212012
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

Guidelines Breast
Version 2017.1

Endocrine and “Targeted” Therapy in Metastatic Breast Cancer

START

Endocrine Therapy of Metastatic Breast Cancer

- **Version 2002:**
  Gerber / Friedrichs

- **Versionen 2003–2016:**
  Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Liedtke / Loibl / Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schneeweiß / Schütz / Stickeler

- **Version 2017:**
  Schmidt / Thill

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Version 2017.1

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Further Information

References

FORSCHEN
LEHREN
HEILEN

Endocrine Therapy in Metastatic Breast Cancer

Indication

Oxford LoE: 1a **GR: A** **AGO: ++**

Endocrine-based 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**

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Further Information

References

Comparison ER/PR and HER2 Metastasis vs. Primary Tumor

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Version 2017.1

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

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References

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Endocrine Therapy
General Considerations

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

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

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Version 2017.1

	Oxford LoE	AGO GR	
➢ GnRHa+ Fulvestrant + Palbociclib	2b	B	++
➢ GnRHa + AI + Palbociclib	5	D	+
➢ 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	+
➢ Aromatase inhibitors without OFS	3	D	- -

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References

Endocrine Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

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***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.**

	Oxford / AGO LoE / GR		
➢ Letrozole + Palbociclib	1b	B	++
➢ Fulvestrant 500 mg + Palbociclib	1b	B	++
➢ Fulvestrant 500 mg	1b	B	++
➢ Aromatase inhibitors (3rd generation)*	1a	A	++
➢ Tamoxifen	1a	A	+
➢ Exemestane + Everolimus	1b	A	+
➢ Tamoxifen + Everolimus	2b	B	+
➢ Letrozole + Everolimus	2b[a]	B	+/-
➢ Fulvestrant + Everolimus	2b[a]	B	+/-
➢ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
➢ Repeat prior treatments	5	D	+/-

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Further Information

References

FORSCHEN
LEHREN
HEILEN

Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab

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	Oxford / AGO LoE	GR	
➢ Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab	1b	B	+/-
➢ Bevacizumab plus endocrine treatment as first line therapy for advanced disease	1b	B	+/-

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Further Information

References

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Version 2017.1

HER2 Positive and HR-Positive Metastatic Breast Cancer

Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

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	Oxford / AGO LoE	GR	
➢ Anastrozole plus trastuzumab	1b	B	+/-
➢ Letrozole plus trastuzumab	2b	B	+/-
➢ Letrozole plus lapatinib	1b	B	+/-
➢ Fulvestrant plus lapatinib	1b	B	+/-
➢ Aromatase inhibitors plus Trastuzumab / Pertuzumab*	2b[a]	B	+/-

Poor efficacy of endocrine therapy alone.

Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

***Study participation recommended**

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Further Information

References

Concomitant or Sequential Endocrine-Cytostatic Treatment

Oxford / AGO
LoE / GR

- **Concomitant endocrine-cytotoxic treatment** — **1b A -**
  - **May increase response rate and progression free interval but not overall survival**
  - **May increase toxicity**
- **Maintenance endocrine therapy after chemotherapy induced response** — **2b B +**
  - **Increases progression free interval**

Endocrine and "Targeted" Therapy in Metastatic Breast Cancer (2/11)

No further information

No references

Endocrine and "Targeted" Therapy in Metastatic Breast Cancer (3/11)

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Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (6/11)

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Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab (8/11)

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Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients (10/11)

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Concomitant or Sequential Endocrine-Cytostatic Treatment (11/11)

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Guidelines Breast
Version 2017.1

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

START

***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

Guidelines Breast
Version 2017.1

- **Version 2002:**
  von Minckwitz / Schaller / Untch

- **Versions 2003–2016:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / von Minckwitz / Möbus / Müller / Rody / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thill / Thomssen

- **Version 2017:**
  Fehm / Jackisch

Guidelines Breast
Version 2017.1

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 to be 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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Version 2017.1

Endocrine Resistance in Metastatic Breast Cancer

Primary endocrine resistance:

- **Relapse within 2 years of adjuvant endocrine treatment (ET)**
- **Progressive disease within first 6 months of first-line ET for MBC**

Secondary endocrine resistance:

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

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References

FORSCHEN
LEHREN
HEILEN

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

Treatment of Metastatic Breast Cancer
Predictive Factors

Guidelines Breast
Version 2017.1

Therapy	Factor	Oxford / AGO LoE	GR	
Endocrine therapy	ER / PR (primary tumor, metastasis)	1a	A	++
	previous response	2b	B	++
Chemotherapy	previous response	1b	A	++
Anti-HER2-drugs	HER2 (primary tumor, better metastasis)	1a	A	++
Bone modifying drugs	bone metastasis	1a	A	++
Any therapy	CTC monitoring	1b	A	+*

(other potentially biological factors see chapter „Predictive factors“)

*Within clinical trials

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References

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

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References

Cytotoxic and Targeted Therapy

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.**

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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**

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Further Information

References

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

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MBC HER2-negative/HR-positive Cytotoxic 1st-Line Therapy*

	Oxford / AGO LoE	GR	
Monotherapy:			
➢ Paclitaxel (q1w), Docetaxel (q3w)	1a	A	++
➢ Doxorubicin, epirubicin, mitoxantrone (A) Peg. liposomal doxorubicin (A_{lip})	1b	A	++
➢ Vinorelbine	3b	B	+
➢ Capecitabine	2b	B	+
➢ Nab-paclitaxel	2b	B	+
Polychemotherapy:			
➢ A + T	1b	A	++
➢ Paclitaxel + capecitabine	2b	B	+
➢ Docetaxel + capecitabine after adj. A	1b	A	+
➢ T + gemcitabine after adj. A	2b	B	++
➢ A + C or A_{lip} + C	1b	B	++

*In ER pos. disease only if endocrine therapy is not or not anymore indicated

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

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	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

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References

MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

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	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	-

*At least one year disese-free after adjuvant treatment

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References

Triple Negative Metastatic Breast Cancer

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	Oxford / AGO LoE	GR	
➢ Experimental therapies within studies			++
➢ Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC			+
➢ Carboplatin (vs. Docetaxel)	1b[a]	B	+/-
➢ in gBRCA mutation	1b[a]	B	+
➢ Gemcitabine/Cisplatin (vs. Gem/Pac)	1b	A	+
➢ Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)	2b[a]	B	+
➢ Bevacizumab added to first line cytotoxic therapy	1b	B	+

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References

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

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	Oxford / AGO LoE / GR		
➢ **1st line in combination with:**			
➢ Paclitaxel (q1w)	1b	B	+
➢ Capecitabine	1b	B	+
➢ Anthracyclines	2b	B	+/-
➢ Nab-Pac	2b	B	+/-
➢ Docetaxel (q3w)	1b	B	+/-
➢ **Cap+Bev as maintenance after Doc+Bev**	1b[a]	B	+/-
➢ **2nd line in combination with:**			
➢ Taxanes	1b	B	+/-
➢ Capecitabine	1b	B	+/-
➢ Gemcitabine or vinorelbine	1b	B	-
➢ **2nd line as treatment through multiple lines**	1b	B	-

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First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

	Oxford / AGO LoE	/ GR	
➢ Docetaxel + trastuzumab + pertuzumab	1b	A	++
➢ Paclitaxel (wk) + trastuzumab + pertuzumab	2b	B	++
➢ Nab-Paclitaxel + trastuzumab + pertuzumab	3b[a]	C	+
➢ Vinorelbine + Trastuzumab + Pertuzumab	3b	B	+
➢ T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)	2b	B	+
➢ 1st 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

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2nd line Therapy of HER2-positive mBC
(If Pretreatment with Trastuzumab)

	Oxford / AGO LoE	/ GR	
➢ T-DM 1	1b	A	++
➢ TBP: 2nd line chemotherapy + trastuzumab	2b	B	+
➢ TBP: 2nd line chemotherapy + trastuzumab + pertuzumab	5	D	+/-
➢ Any other 2nd line chemotherapy* + trastuzumab + pertuzumab	5	D	+/-
➢ Taxane + trastuzumab + pertuzumab	5	D	+
➢ Capecitabine + trastuzumab + pertuzumab	1b[a]	B	+/-
➢ Capecitabine + lapatinib	1b	B	+
➢ Trastuzumab + lapatinib (HR neg. disease)	2b	B	+

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

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Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

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	Oxford / AGO LoE	GR	
Pretreatment with Trastuzumab			
➢ **T-DM 1**	1b	A	++
➢ **Capecitabine + lapatinib**	1b	B	+
➢ **Vinorelbine + lapatinib**	2b	B	+/-
➢ **Trastuzumab + lapatinib (HR neg. disease)**	2b	B	+
➢ **Chemotherapy + trastuzumab *(„treatment beyond progression“)***	2b	B	+
➢ **Trastuzumab + pertuzumab**	2b	B	+
➢ **Vinorelbine + trastuzumab + everolimus *(trastuzumab resistant, taxane pretreated)***	1b	B	+/-
Neither data for patients pretreated with trastuzumab and pertuzumab nor data for treatment beyond progression available.			
➢ **Experimental anti-HER2-regimen**	5	D	+
➢ **For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.**	5	D	+

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Lapatinib in HER2-positive Metastatic Breast Cancer

	Oxford / AGO LoE / GR		
In combination with			
➢ **Trastuzumab for heavily pre-treated pts (HR negative)**	**2b**	**B**	**+**
➢ **Paclitaxel in 1st line**	**1b**	**B**	**+/-**
➢ **Capecitabine in > 2nd line**	**1b**	**B**	**+**
➢ **Vinorelbine**	**2b**	**B**	**+/-**
➢ **AI in ER positive disease**	**2b**	**B**	**+/-**
➢ **In patients with brain metastases (radioresistance) in combination with capecitabine**	**2b**	**B**	**+/-**

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Immunodiagnostic Tests and Immunotherapy*

	Oxford / AGO LoE	/ GR	
Immunodiagnostic tests:			
Immunological parameters in peripheral blood	**5**	**D**	**--**
Local immunotherapy			
➢ **Imiquimod topically for skin metastases**	**4**	**C**	**+/-**
Systemic immunotherapy - including items below – only within clinical trials:			**++**

- **HER2-vaccination in high risk population**
- **Immunomodulation (e.g. addition of Nov-2 to AC –T)**
- **Dendritic cell intradermal vaccination**
- **Active vaccination**
- **Passive vaccination**
- **Therapy with oncolytic viruses**
- **Cytokines**
- **Checkpoint inhibitors (PD1; PDL-1;…)**

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Further Information

References

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***Study participation recommended**

Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/19)

No further information

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Update since 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).

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No further information

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Endocrine resistance in metastatic breast cancer (4/19)

No further information

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No further information

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Cytotoxic Therapy Goals (6/19)

No further information

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Cytotoxic and Targeted Therapy (7/19)

No further information

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Cytotoxic Therapy Duration (8/19)

No further information

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No further information

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MBC HER2 negative Cytotoxic 1st-Line Therapy (10/19)

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MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (11/19)

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Suggested after anthracyclines (in alphabetical order): Capecitabine, docetaxel, study-integrated experimental therapies, pegylated 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 breats cancer (Ghersi 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 (Ghersi et al, 2015; Ravdin et al, 2003). Due to different toxicity profiles of each substance individual indication is needed.

Docetaxel in combination with pegylated doxorubicin was superior to docetaxel alone in a randomised phase III trial (Sparano et al. 2009). It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantag fro m 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.

MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (12/19)

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Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (13/19)

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Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (14/19)

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First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (15/19)

No further information

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Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab) (16/19)

No further information

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T-DM1

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TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)

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TBP: 2nd-Line chemotherapy + Trastuzumab + pertuzumab (Treatment beyond progression)

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Any other 2nd-Line chemotherapy + trastuzumab + pertuzumab

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Taxane + trastuzumab + pertuzumab

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Capecitabine + lapatinib

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Trastuzumab + lapatinib vs lapatinib

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Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (17/19)

No further information

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Trastuzumab + lapatinib vs lapatinib

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TBP: 2nd-line chemotherapy + trastuzumab

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Lapatinib in HER2-positive Metastatic Breast Cancer (18/19)

No further information

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Taxanes+ lapatinib

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Vinorelbine + Lapatinib:

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Lapatinib + aromatase inihibitors (if ER+)

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Immunodiagnostic Tests and Immunotherapy (19/19)

No further information

No references

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Osteooncology and Bone Health

START

Osteooncology and Bone Health

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- **Versions 2002-2016:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Hanf / Huober / Jackisch / Janni / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon
- **Version 2017:**
  Diel / Liedtke

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 osseous progression	5	D	++

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Further Information

References

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LEHREN
HEILEN

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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 while on bisphosphonates**	4	C	+/-

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Further Information

References

CALGB 70604: Longer-Interval vs Standard Dosing of Zoledronic Acid

- 1822 patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma, 795 completed the study

- SRE within 2 yrs: 29.5 % zoledronic acid every 4 weeks
  28.6 % zoledronic acid every 12 weeks

Himelstein et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58.

Bone Modifying Agents for the Therapy of Bone Metastases

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Further Information

References

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	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	+
➢ 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	- -

Skeletal Metastases
Treatment with Radionuclids

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	Oxford / AGO LoE / GR		
➢ **Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisit: hot spots in the bone scintigraphy)**	**1b**	**B**	**+**
➢ **^{186}Rhenium-hydroxyethylidene-diphosphonat**	**2b**	**B**	**+**
➢ **^{153}Samarium**	**1b**	**B**	**+**
➢ **^{89}Strontium**	**1b**	**B**	**+**
➢ **^{223}Radium**	**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**

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Bone Metastases
Acute Spinal Cord Compression / Paraplegia

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	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	++

Clinical trials have included patients with different tumor entities!

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References

Surgery for Bone Metastases

Technical Aspects

Spine and limbs

Oxford LoE: 3b **GR: C** **AGO: +**

- **Marrow splints**
- **Plate osteosynthesis**
- **Compound osteosynthesis (replacement by PMMA and osteosynthesis)**
- **Vertebral replacement by titanspacer**
- **Tumor-Endoprothesis**
- **Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor**
- **Kypho-IORT (in studies only)***
- **Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)**

*Study participation recommended

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References

Metastatic Bone Disease: Radiotherapy (RT)

Bone metastases

	Oxford / AGO LoE / GR		
➢ With fracture risk	1a	B	++
➢ With functional impairment	1a	B	++
➢ With bone pain	1a	B	++
➢ Single dose RT = fractionated RT	2a	B	++
➢ With neuropathic bone pain	1b	B	++
➢ Asymptomatic isolated bone metastases	5	D	+/-
➢ Reduction of radiation induced pain flare by dexamethasone	1b	B	+

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.**

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Further Information

References

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

	Oxford LoE
➢ **Renal function deterioration due to IV-aminobisphosphonates**	**1b**
➢ **Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3 % / 1.8 %)**	**1b**
➢ Association with (simultaneous) anti-angiogenetic therapies	**3b**
➢ **Severe hypocalcemia (Dmab > BPs)**	**1b**
➢ **Acute Phase Reaction (IV Amino-BPs, Db) 10–30 %**	**1b**
➢ **Gastrointestinal side effects (oral BPs) 2–10 %**	**1b**
➢ **Atypical femur fractures** (absolute risk of 11 per 10,000 person years of BP use)	**2b**

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Recommendations for Prevention of Osteonecrosis of the Jaw (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

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References

Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage

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	Oxford / AGO LoE / GR		
Clodronate (oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Aminobisphosphonates (iv or oral)			
Postmenopausal patients	1a	A	+
Premenopausal patients	1a	B	+/-
Denosumab (60 mg s.c., q6mo)			
Postmenopausal patients	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 definded; in adjuvant studies duration of BP treatment varied from 2–5 years**

Aminobisphosphonates include:
Zoledronic acid (65 %), oral ibandronate (24 %), oral pamidronate (8 %), oral risedronate (2 %), oral alendronate (1 %) (data from EBCTCG-metaanalysis)

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References

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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	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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References

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

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Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

	Oxford / AGO LoE / GR		
➢ Physical activity	4	C	++
➢ Avoiding immobilisation	4	C	++
➢ Calcium (1000–1500 mg/d)**	4	C	++
➢ Vitamine D3 suppl. (800–2000 U/d)	4	C	++
➢ Cessation of smoking, reduction of alcohol	2b	B	++
➢ Avoiding BMI < 20 mg/m^2	3b	C	++
➢ Drugs approved for the treatment of osteoporosis in adults (see next slide)			

*http://www.dv-osteologie.org/dvo_leitlinien/osteoporose-leitlinie-2014
**if nutritional supply is insufficient, (in combination with Vit D3 only)

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References

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Medical Treatment of Osteoporosis

	Oxford / AGO LoE / GR		
➢ Alendronate 70 mg po/w*	1b	B	++
➢ Denosumab 60 mg sc/6m*	1b	B	++
➢ Ibandronate 150 mg po/m*	1b	B	++
➢ Ibandronate 3 mg iv/3m	1b	B	++
➢ Parathyroid hormone (1-84) 100 µg sc/d	1b	B	+
➢ Raloxifene 60 mg po/d (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	++

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* Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis
**Elevated risk of myocardial infarction. Substance restricted to postmenopausal pats. with severe osteoporosis and high risk of fractures

http://www.dv-osteologie.org/uploads/Leitlinie%202014/DVO-Leitlinie%20Osteoporose%202014%20Kitteltaschenversion%2015.12.2014.pdf

TABELLE 4.2.: INDIKATION FÜR EINE MEDIKAMENTÖSE 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 ≥ 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)

Photo Courtesy of the DVO

Osteooncology and Bone Health (2/20)

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No further information

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Specific Sites of Metastases

START

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Specific Sites Of Metastases
Local Approaches to Metastatic Disease

- **Version 2002:**
  Dall / Fersis / Friedrich
- **Versionen 2003–2016:**
  Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Fehm / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Lux / Maass / Oberhoff / Rezai / Schaller / Schütz / Seegenschmiedt / Solomayer / Souchon
- **Version 2017:**
  Thomssen / Bischoff

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Specific Sites of Metastases

- **Liver and lung metastases**
- **Malignant pleural and pericardial effusions**
- **Ascites**
- **Bone marrow involvement**
- **Soft tissue metastases**
- **Any other organs**

- **Consider also chapter „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“**

General Aspects
Surgery or Ablation of Metastases

	Oxford / AGO LoE / GR		
➢ Histological / cytological verification	3	B	+
➢ Systemic treatment preferred	2a	B	++*
➢ Consider surgery only in case of good response to palliative treatment	2b	C	+
➢ Metastases surgery is an option for pts in good conditions with late onset oligometastases	3a	B	+
➢ Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression	5	D	+/-
➢ Systemic treatment after surgery	5	D	++

*** See chapters with systemic treatment recommendations**

Local Therapy in Primary Metastatic Disease

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	Oxford / AGO LoE / GR		
➢ **Surgery (R0) of the primary tumor**			
➢ In case of bone metastases only	2b[a]	B	+/-
➢ In case of visceral metastases	2b[a]	B	-
➢ **Axillary surgery for cN1**	5	D	+/-
➢ **Sentinel if cN0**	5	D	-
➢ **Radiotherapy of the primary tumor**			
➢ Alone (without surgery)	3a	C	+/-
➢ After local surgical treatment with BCS or mastectomy (acc. adjuvant indication)	3a	C	+

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Further Information

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Liver Metastasis
Local Therapy

	Oxford / AGO LoE / GR		
➢ **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)			

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Pulmonary Metastases
Local Therapy

	Oxford / AGO LoE	GR	
➢ Before any surgery: staging and biopsy (CT-guided FNA / CNB or transbronchial FNA)	3a	B	+
➢ Resection of pulmonary metastases by VATS or conventional resection			
➢ In case of multilocular metastatic disease	3a	B	-
➢ In case of single / few unilateral metastases 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))

*VATS = video-assisted thoracic surgery

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Further Information

References

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 [dsypnea (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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References

Malignant Ascites
Local Therapy

	Oxford / AGO LoE	GR	
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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References

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Malignant Pericardial Effusion
Local Therapy

	Oxford / AGO LoE	Oxford / AGO GR	
Symptomatic pericardial effusion:			
➢ **Drainage, fenestration**	**3b**	**B**	**++**
➢ **Combination with optimized systemic therapy**	**4**	**C**	**++**
➢ **VATS (video-assisted thoracic surgery)**	**4**	**C**	**+**
➢ **Ultrasoung guided puncture and instillation of cytotoxic compounds**			
➢ **Bleomycin, cisplatinum, mitomycin C, mitoxantrone etc.**	**4**	**C**	**+/-**
➢ **Bevacizumab**	**4**	**C**	**+/-**

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Further Information

References

Bone Marrow Infiltration Associated with Pancytopenia

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	Oxford / AGO LoE / GR		
➢ **Weekly chemotherapy with*:**			
➢ **Epirubicin, Doxorubicin, Paclitaxel**	**4**	**D**	**++**
➢ **Capecitabine**	**4**	**D**	**++**
➢ **HER2 pos.: add anti-HER2 -treatment**	**5**	**D**	**++**

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* Consider pre-treatment

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Soft Tissue Metastasis
Local Therapy

	Oxford / AGO LoE	GR	
➢ **Surgery of locoregional limited metastases (skin, muscular, nodal) with complete resection (R0) after exclusion of further metastases**	4	C	+
➢ **Radiotherapy (after surgery or, if immediate surgery is not indicated):**			
➢ **Soft tissue metastases**	3b	C	+
➢ **Paresis, spinal cord compression**	2b	C	++
➢ **Plexus infiltration**	3b	C	++

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Further Information

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Specific Sites of Metastases (2/13)

No further information

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Pubmed 1.1.2016 bis 31.1.2017

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No references

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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 +)

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

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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
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4. Eichler K et al. Transarterial chemoembolisation (TACE) with gemcitabine: phase II study in patients with liver metastases of breast cancer. Eur J Radiol. 2013;82(12):e816-22
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.
5. Vogl TJ, et al. Magnetic resonance-guided laser-induced interstitial thermotherapy of breast cancer liver metastases and other noncolorectal cancer liver metastases: an analysis of prognostic factors for long-term survival and progression-free survival. Invest Radiol. 2013;48(6):406-12.

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.
2. Rena O, et al: The role of surgery in the management of solitary pulmonary nodule in breast cancer patients. Eur J Surg Oncol. 2007 Jun;33(5):546-50.
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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6. García-Yuste M, Pulmonary metastasectomy in breast cancer. J Thorac Oncol. 2010 Jun;5(6 Suppl 2):S170-1.
7. Nichols FC Pulmonary metastasectomy Thorac Surg Clin. 2012 Feb;22(1):91-9, REVIEW
8. Omar M. Rashid and Kazuaki Takabe The evolution of the role of surgery in the management of breast cancer lung metastasis. J Thorac Dis. 2012 August; 4(4): 420–424. REVIEW
9. Kycler W, Laski P: Surgical approach to pulmonary metastases from breast cancer. Breast J. 2012 Jan;18(1):52-7.

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11. Fan J, Chen D, Du H, Shen C, Che G. Prognostic factors for resection of isolated pulmonary metastases in breast cancer patients: a systematic review and meta-analysis. J Thorac Dis. 2015 Aug;7(8):1441-51. doi: 10.3978/j.issn.2072-1439.2015.08.10.
12. Lumachi F, Mazza F, Del Conte A, Lo Re G, Ermani M, Chiara GB, Basso SM. Anticancer Res. 2015 Jun;35(6):3563-6. Erratum in: Anticancer Res. 2015 Jul;35(7):4371. Short-term Survival of Patients with Lung Metastases from Colorectal and Non-colorectal Cancer Who Underwent Pulmonary Metastasectomy.

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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6. Guerrini GP, Lo Faso F, Vagliasindi A, Lembo R, Solaini L, Soliani P, Taviani M, Porrello C. The Role of Minimally Invasive Surgery in the Treatment of Lung Metastases. J Invest Surg. 2016 Oct 3:1-6.
7. Meyer C, Bartsch D, Mirow N, Kirschbaum A. Video-Assisted Laser Resection of Lung Metastases-Feasibility of a New Surgical Technique. Thorac Cardiovasc Surg. 2017 Jan 22.

Malignant Pleural Effusion - Local Therapy (9/13)

Further information and references:

2016 Vote result of the AGO recommendation (complete slide without further changes): yes = 19/ no = 1

With regard to quality of life, in several cohorts a rather good effects of patient-controlled pleural drainage using an indwelling catheter was demonstrated. A small and well designed trial has demonstrated substantially higher efficacy and improved 30-days activity in patients with pleural drainage compared to patients with pleurodesis. The ABC3-recommendations considered continous pleural drainage for at least equivalent to pleurodesis..

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.

3. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews 2004,
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
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9. Ibrahim IM, Dokhan AL, El-Sessy AA, Eltaweel MF. Povidone-iodine pleurodesis versus talc pleurodesis in preventing recurrence of malignant pleural effusion. J Cardiothorac Surg. 2015 May 1;10:64. doi: 10.1186/s13019-015-0270-5.

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, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, Wang X, Archer L, Veit LJ, Kohman L; Cancer and Leukemia Group B. Optimal management of malignant pleural effusions (results of CALGB 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.
4. Warren WH, Kalimi R, Khodadadian LM, Kim AW. Management of malignant pleural effusions using the Pleur(x) catheter. Ann Thorac Surg. 2008 Mar;85(3):1049-55.
5. Hak CC, Sivakumar P, Ahmed L. Safety of indwelling pleural catheter use in patients undergoing chemotherapy: a five-year retrospective evaluation. BMC Pulm Med. 2016 Mar 11;16:41.

Statement: Systemic treatment after pleurodesis (3b C +/-)

Statement: Local antibody therapy (i.e. Catumaxomab) (3b C -)

1. Sebastian M, Kiewe P, Schuette W, Brust D, Peschel C, Schneller F, Rühle KH, Nilius G, Ewert R, Lodziewski S, Passlick B, Sienel W, Wiewrodt R, Jäger M, Lindhofer H, Friccius-Quecke H, Schmittel A. 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. 2013 Dec;8(4):291-4.
4. Kurbacher CM, Horn O, Kurbacher JA, Herz S, Kurbacher AT, Hildenbrand R, Bollmann R. Outpatient Intraperitoneal Catumaxomab Therapy for Malignant Ascites Related to Advanced Gynecologic Neoplasms. Oncologist. 2015 Nov;20(11):1333-41.

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 possibel.

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.
7. Saltzman AJ, Paz YE, et al, Comparison of Surgical Pericardial Drainage With Percutaneous Catheter Drainage for Pericardial Effusion, J Invasive Cardiol. 2012 November ; 24(11): 590–593.
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 cabecitabine) 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.

6. Artac M, Koral L, Toy H, Guler T, Boruban MC, Altundag K. Complete response and long-term remission to anti-HER2 combined therapy in a patient with breast cancer presented with bone marrow metastases. J Oncol Pharm Pract. 2014 Apr;20(2):141-5.
7. Pahouja G, Wesolowski R, Reinbolt R, Tozbikian G, Berger M, Mangini N, Lustberg MB.: 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.

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CNS Metastases in Breast Cancer

START

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CNS Metastases in Breast Cancer

- **Versions 2003–2016:**
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  In collaboration with:

  P. Feyer und D. Rades (DEGRO)

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CNS Metastases in Breast Cancer – Incidence

- **Breast cancer is the 2nd most common cause of CNS metastases**
- **At autopsy:**
  - **Parenchymal CNS metastases: ~30–40%**
  - **Leptomeningeal CNS metastases: ~ 5–16%**
- **Increasing incidence (10 % ⇨ 40 %)**
- **Increasing incidence due to**
  - **More effective treatment of extracerebral sites with improved prognosis**
  - **Increasing use of MRI in diagnostic evaluation**
- **Lack of 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**
  - **Molecular subtype (Luminal B, HER2 positiv, triple-negative)**

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

There is no evidence for BM-screening in asymptomatic BC-patients

Graded Prognostic Assessment (GPA) Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

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

Median survival by GPA:
GPA 0-1.0 = 3.4 months
GPA 1.5-2.0 = 7.7 months
GPA 2.5-3.0 = 15.1 months
GPA 3.5-4.0 = 25.3 months

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

Sperduto PW. J Clin Oncol 2012, 30:419-425

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References

Rades Score* - Worksheet to Estimate Survival from Brain Metastases (BM) by plus chemotherapy Diagnosis

	6-months survival rate(%)	**Score**
Prognostic Factor		
age ≤ 60 years ≥ 61 years	 43 25	 4 3
Karnofsky-Index < 70 ≥ 70	 8 53	 1 5
Extracranial metastases no yes	 51 24	 5 2
Interval from first diagnosis to WBRT ≤ 8 months > 8 months	 32 36	 3 4

Median survival by Rades-Score:
Rades-Score 9-10 = 2 months
Rades-Score 11-13 = 3 months
Rades-Score 14-16 = 5 months
Rades-Score 17-18 = 12 months

*Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed, validated in 350 new patients

Rades et al., STO 2008
Dziggel et al., STO 2013

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Single / Solitary Brain Metastasis

	Oxford/AGO LoE	GR	
Local therapy alone: SRS (≤ 4 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**	**+**
Hippocampal-sparing	**2b**	**C**	**+/-**

- **WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms, but has no survival benefit. WBRT impaires neurocognitive function.**
- **In case of resection of the tumor the tumorbed 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

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References

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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	+
Hippocampal-sparing	2b	C	+/-

- **WBRT in addition to SRS/FSRT or tumor resection improves local control and symptoms, but has no survival benefit. 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

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Further Information

References

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

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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. JAMA. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839**

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

Guidelines Breast
Version 2017.1

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.

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Further Information

References

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Possible Factors for Decision Making Neurosurgery versus Stereotactic Radiosurgery

Guidelines Breast
Version 2017.1

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:

- Tumor location poorly amenable to surgery
- More than four lesions

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References

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Version 2017.1

Multiple Brain Metastases >3 (4) Lesions

	Oxford / AGO LoE / GR		
➢ WBRT (supportive steroids*)	1a	A	++
➢ SRS/FSRT	4	C	+/-
➢ Hippocampal-sparing radiotherapy	2b	C	+/-
➢ Radiochemotherapy for cerebral disease control	3b	C	-
➢ Chemotherapy alone	3a	D	+/-
➢ Corticosteroids alone*	3a	B	+/-
➢ Re-irradiation if recurrence**	4	C	+/-

SRS = stereotactic radiosurgery
FSRT = fractionated stereotactic radiotherapy
WBRT = whole brain radiotherapy

*** adapted to symptoms**

**** can be discussed depending on the time-intervall from first radiation, prior dose and localization**

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References

Systemic and Symptomatic Therapy of Brain Metastases*

Guidelines Breast
Version 2017.1

	Oxford / AGO LoE	GR	
➢ Continuation of the actual systemic therapy if first diagnosis of brain metastases and stable extracranial disease	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	++

* In addition to local therapy

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References

Leptomeningeal Carcinomatosis
Local Therapy

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	Oxford / AGO LoE / GR		
Intrathecal or ventricular therapy			
➢ MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)	2b	B	++
➢ Liposomal cytarabine 50 mg, q 2w	3b	C	++
➢ Thiothepa	3b	C	+
➢ Steroids	4	D	+/-
➢ Trastuzumab (HER2 pos. disease)	4	C	+/-
Radiotherapy			
➢ Focal (bulky disease)	4	D	+
➢ WBRT	4	D	+
➢ Neuroaxis (disseminated spinal lesions)	4	D	+/-

Due to bad prognosis consider best supportive care, especially in patients with poor performance status

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Further Information

References

CNS Metastases in Breast Cancer (2/14)

No further information

No references

CNS Metastases in Breast Cancer – Incidence (3/14)

No further information

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CNS Metastases in Breast Cancer (BC) Risk Factors (4/14)

Further information:

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an "unmasking" of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

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Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis (5/14)

No further information

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Rades OS-Score (6/14)

No further information

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Single / Solitary Brain Metastases (7/14)

Further information

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was described to be more frequent with the addition of WBRT to SRS. Adjuvant WBRT does not improve overall survival 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.

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Brain Metastases 2-3 (2-4) lesions (8/14)

No further information

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See references Slide 7

NCCTG N0574 (Alliance): (9/14)

No further information

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EORTC 22952- 26001 Study (10/14)

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Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (11/14)

No further information

No references

Multiple Brain Metastases (12/14)

No further information

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Systemic and Symptomatic Therapy of Brain Metastases (13/14)

Further information:

In the single-arm phase II trial (Landscape) 45 patients received capecitabine in combination with lapatinib to prolong the time until WBRT. 29 patients had an objective CNS response (65.9%, 95% CI 50.1-79.5); all were partial responses with 49% of patients experiencing a grade 3or4 treatment-related adverse events. Therefore, the landscape trial proves that systemic therapy can prolong the time until local therapy of BM is necessary but no general recommendation for this combination therapy can be made. Several retrospective trials show that T-DM1 is safe in patients with brain metastases In a subcohort of the Kamilla trial 21% of patients after local treatment for BM or asymptomatic brain metastases experienced a complete or partial remission with T-DM1. No newly developed targeted therapy could prove to be superior to other cytotoxic agents in the brain.

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Leptomeningeal Carcinomatosis Local Therapy (14/14)

No further information

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Trastuzumab intrathecal

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MTX high dose

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Complementary Therapy

Survivorship

Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

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- **<u>Versionen 2002–2016:</u>**
  Albert / Bauerfeind / Blohmer / Fersis / Friedrich / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

- **<u>Version 2017:</u>**
  Gerber / Lück

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„Alternative“ Therapies

„Integrative Oncology“

„Unconventional methods“

CAM
Complementary + alternative medicine

UCT
Unconventional **Thx**

Complementary	Alternative	Unconventional
In addition to scientifically based medicine	*Instead of scientifically based medicine*	*Unproven outsider methods*

Problems of available studies: selection bias, small case numbers, short follow-up, contrary results etc.

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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

	Oxford LoE	AGO GR	
Preoperative:			
➢ Hypnosis (reduces anxiety, pain, nausea)	1b	B	+
Postoperative:			
➢ Acupuncture (pain relief, anxiety)	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	-

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Complementary Treatment
Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

	Oxford LoE	AGO GR	
➢ **Mistletoe (Viscum album)** in order to reduce side effects	1a	B	+/-
➢ **Thymic peptides** lowered risk of severe infections	2a	B	+/-
➢ **Ginseng** in order to reduce cancer related fatigue; note: 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	--
- Improvement of cancer related fatigue	1b	B	-
➢ **Curcumin** as an adjunct to reduce radio dermatitis	1b	B	+/-
➢ **Ginger** for chemotherapy induced nausea & vomiting	1b	C	+/-

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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 (fatique, QoL)	1b	B	-
➢Proteolytic enzymes in order to reduce chemotherapy-induced toxicity		3b	B
➢Chinese herbal medicine improves wound healing	1b	B	-*inf
➢Oxygen and ozone therapy	5	D	- -

*inf: i.v.-infusion (in Germany not approved)

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Additional Complementary Therapy

Side Effects Related to Cancer Treatments e.g. Chemotherapy

	Oxford LoE	AGO GR	
➢ **Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients**	1b	B	-
➢ **Homoeopathic medicines for adverse effects of cancer treatments**	1b	B	+/-
➢ Topical calendula (>= 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 >=nausea and vomiting	1a	B	+
➢ Cognitive dysfunction	5	D	+/-
➢ Fatigue	1a	B	+
➢ Pain	1a	B	+/-
➢ Leucopenia (Moxibustion)	2b	B	+/-
➢ Hot flashes	2b	B	+
➢ Treatment of chemotherapy induced polyneuropathy	2b[a]	B	-

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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 fatique, no higher risk of lymphedema**	1a	A	++

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Complementary Treatment
Mind-Body Medicine II

	Oxford / AGO LoE / GR
➢ **Yoga** • Improves sleep, quality of life, stress, anxiety, depression, fatigue	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 +

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Modifiable Lifestyle Factors
Prevention of Recurrence/ Improvement of Overall Survival I

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	Oxford / AGO LoE / GR		
➢ **Physical exercise** (Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)	1a	A	++
➢ **Smoking**	2b	A	+/-
➢ **Alcohol consumption (>6 g/day)**	2b	A	+/-

Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis

Prevention of Recurrence / Improvement of Overall Survival II

	Oxford /AGO LoE	GR	
➢ **Adherence to normal BMI/weight loss if overweight, irrespective of HR-status**	1a	A	++
➢ **Low fat diet** dietary counseling recommended	1a	A	+
➢ **Avoid high-fat dairy food**	2b	C	+
➢ **Flaxseed / increased fibre intake**	2a	B	+
➢ **Adherence to general nutrition guidelines (e.g. DGE, WCRF)**	2a	B	++
➢ **Dietary extremes**	1b	B	- -

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Complementary Treatment

Prevention of Recurrence / Improvement of Overall Survival III

Dietary Supplements – Herbal Therapies

	Oxford LoE	AGO GR	
Post treatment vitamin/antioxidant supplements doesn't appear to be associated with increased risk of recurrence (beware of drug/treatment interactions)	2b	B	
Smokers on antioxidant supplements are at higher risk for lung cancer	1b	A	
For Prevention of BC Recurrence:			
➢ **Antioxidants**	2a	B	+/-
➢ **Orthomolecular substances (Selenium, Zinc...)**	5	D	-
➢ **Vitamine supplementation in pts on a balanced diet (esp. Vit C, E, D)**	2a	B	+/-
➢ **Artificial carotenoids appear to be associated with worse outcome**	2b	B	-
➢ **Proteolytic enzymes (Papain, Trypsin, Chymotrypsin)**	3b	B	-
➢ **Soy-food (natural source of phytoestrogenes)**	2a	B	+/-
➢ **Concentrates containing ≥ 100 mg) isoflavones**	2a	B	-
➢ **Black Cohosh (Cimicifuga racemosa)**	2a	B	+/-
➢ **Mistletoe (Viscum album)**	1b	C	-
➢ **Thymic peptides (impact on OS)**	2a	B	-
➢ **Oxygen- and ozone therapy**	5	D	- -
➢ **Antioxidant supplements (after completion of radiotherapy)**	2b	B	+/-
➢ **Laetrile**	1c	D	- -
➢ **Methadon**	5	D	- -
➢ **Cancer bush (Sutherlandia frutescens), Devil's claw (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis), Bambara groundnut (Vignea subterranean)**	5	D	-

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Further Information

References

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Complementary Treatment
Cancer Pain Reduction

Guidelines Breast
Version 2017.1

	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			

Complementary Therapy – Survivorship (2/14)

Further information:

Screened Data Sources:

Pubmed	2012 - 01/2017
ASCO	2015 – 2016
SABCS	2015 – 2016
EBCC	2015 – 2016
Cochrane library:	summary Jan. 2017:

No references

Alternative Therapies (3/14)

Further information:

The term „alternative therapies“ has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.

- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

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General Considerations (4/14)

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Complementary Treatment. Treatment phase. Impact on Toxicity I (6 /14)

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Gynaecological Issues in Breast Cancer Patients

START

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Gynaecologic Issues in Breast Cancer Patients

- **Version 2015:**
  Loibl / Gerber
  (with contribution from Hanf / Kümmel und Stickeler / Scharl)

- **Version 2016:**
  Albert / Bauerfeind / Fersis / Thill

- **Version 2017:**
  Hanf / Scharl

Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

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	Oxford / AGO LoE / GR
➢ **Endocrine responsive disease (receptor pos.)** (HT may increase risk)	**1b B -**
➢ **Endocrine non-responsive disease (receptor neg.)** (apparently no risk increase)	**2a B +/-**
➢ **Endocrine responsive disease (receptor pos.): combined treatment TAM plus low-dose-HT**	**2b B +/-**
➢ **Tibolone**	**1b A - -**
➢ **Topical vaginal application of**	
➢ **Estriol (E3 0,03 mg as treatment course*)**	**4 D +/-**
➢ **Estradiol (E2) during AI therapy**	**4 C -**

***course: 4 weeks daily 1x1, further 8 weeks: 3 x 1 per week**

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Further Medical Approaches to Reduce Menopausal Symptoms I

	Oxford / LoE	AGO / GR	
Medical approaches:			
➢ **Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients**			
➢ **1st choice: venlafaxine**	**1a**	**A**	**+**
➢ **2nd choice: desvenlafaxine**	**1b**	**A**	**+/-**
➢ **3rd choice: sertraline, escitalopram**	**1b**	**A**	**+/-**
➢ **Gabapentin (patients using TAM)**	**1a**	**A**	**+**
➢ **Pregabalin**	**1b**	**A**	**+/-**
➢ **Clonidine (patients using TAM)**	**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

* Complementary and Alternative Medicine

While anti-cancer treatment: Beware of drug interactions!

	Oxford / AGO LoE	GR	
➢ **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-therapy) (pharmacokinetic interference with endocrine therapy, cyctotoxic 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
Integrative Oncology Aspects

	Oxford / LoE	AGO GR	
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 (neo)-Adjuvant Chemotherapy (CT)

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	Oxford / AGO LoE / GR		
➢ **For ovarian function protection**			
CT + GnRHa (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)	1a	B	+
➢ **Fertility preservation counselling**	4	C	++
➢ **Fertility preservation using assisted reproduction therapy (ART) (further information www.fertiprotect.de)**	4	C	+

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References

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 predicitve 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
Sverrisdottr 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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Further Information

References

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HEILEN

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Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, Levaggi A, Giraudi S, Lambertini M, D'Alonzo A, Canavese G, Pronzato P, Bruzzi P. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun;40(5):675-83

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 (I2 = 47.1%, $P_{heterogeneity}$ = 0.026).

Phase III Studies, Investigating Role of LH-RHa for Prevention of Premature Ovarian Failure

Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, Levaggi A, Giraudi S, Lambertini M, D'Alonzo A, Canavese G, Pronzato P, Bruzzi P. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014 Jun;40(5):675-83

Phase IIII studies evaluated

- Li M et al.
- Badawy et al.
- Sverrisdottir et al.
- Del Mastro et al.
- Gerber et al.
- Sun et al.
- Munster et al.
- Elgindy et al.
- Song et al.
- Karimi-Zarchi et al.
- Li JW et al.
- Moore et al.

Testing Ovarian Reserve

	Oxford / LoE	AGO 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**	**+**

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* 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 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	• **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)	• **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)	• **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
Options after Diagnosis of Breast Cancer

	Oxford / AGO LoE / GR		
➢ **Copper intrauterine device (Cu-IUD)**	5	D	+
➢ **Levonorgestrel, Ulipristal orally**	5	D	+

Sexual Health

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	Oxford / LoE	AGO GR	
➢ Assessment of sexual dysfunction	5	C	+
➢ Use of patient-reported questionnaires	4	C	+
➢ Vaginal dryness: Non-hormonal lubricans / moisturizers	1b	B	+
➢ Psychoeducational support, group therapy, sexual counseling, marital counseling, psychotherapy	1b	B	+

Assessment of Sexual Health

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- **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 dissatified 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?

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Further Information

References

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Gynecological Issues in Breast Cancer Patients (2/17)

Further information:

Screened data bases:

- Pubmed 2009 –2016
- ASCO 2009 - 2016
- Cochrane 2009 - 2016
- Medline 2009 - 2016

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

No references

Hormonal (Replacement) Therapy of Estrogen Deficiency after Diagnosis of Breast Cancer (3/17)

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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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. For urogenital problems vaginal moisturizers, isoflavone or topical estrogens can be used.

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7. American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, Farrell R. ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstet Gynecol. 2016 Mar;127(3):e93-6

Further Medical Approaches to Reduce Menopausal Symptoms I (4/17)

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 symproms the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin is considered effective in treating hot flashes. The use of paroxetine and fluoxetine should be avoided because the may reduce the efficacy of tamoxifen. Increased breast cancer mortality is associated with the use of paroxetine and tamoxifen. Patients not being treated with tamoxifen the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes. Breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes. Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes.

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SSRI:

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Fluoxetine

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Citalopram

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Gabapentin

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Pregabalin

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(D) MPA (depo-) (Medroxyprogesterone acetate)

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Vitamine E

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CAM-Approaches to Reduce Menopausal Symptoms II (5/17)

Further information and references:

The majority of studies, regarding the efficacy of herbal treatments for menopausal symptoms – mostly hot flushes – have not been conducted in women with breast cancer and many are of short duration. 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. 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.

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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 (≥100mg) isoflavones can be recommended for breast cancer patients (Fritz H, 2013).

Topical administration of soy-derieved 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.

Red clover-derived 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.

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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

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Taken together neither Black cohosh (Cimicifuga racemosa) nor St John's Wort nor Ginseng root showed a benefit regarding improvement of menopausal symptoms.

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A combination of sodium selenite, proteolytic plant enzymes (bromelaine and papain), and Lens culinaris lectin as a complementary treatment was effective in reducing hormonal treatment related athralgia and mucosal dryness. But there were no reduction in other menopausal symptoms.

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General Approaches to Reduce Menopausal Symptoms III - Integrative Oncological Aspects (6/17)

Further information:

Physical exercises (PE) and cognitive behaviroal 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. The CBT and PE are cost-effective. Prescribtion is recommended by the authors.
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. 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.

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Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/17)

No further information

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Ovarian function protection

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Ovarian Function Preservation - Comparison of Randomized Trials (8/17)

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 and 10/17)

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.“

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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

Phase III Studies Evaluating the Role of LH-RHa in the Preservation of Ovarian Function (11/17)

No further information

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Testing Ovarian Reserve (12/17)

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.
Low AMH (antimuellerian hormone) levels seem to be indicative for reduced ovarian reserve and chemotherapy-related amenorrhea (CRA) in chemotherapy-treated breast cancer patients.
Antral follicle count, defined as the sum of follicle diameters of all follicles of 10mm in both ovaries.

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Assessment of Ovarian Reserve (13/17)

No further information

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Contraceptive Options for Women after Diagnosis of Breast Cancer (14/17)

No further information

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Emergency Contraception - Options after Diagnosis of Breast Cancer (15/17)

No further information

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Sexual Health (16/17)

No further information

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Assessment of Sexual Health (17/17)

Further information:

Sexual Complaints Screener (SCS) for women
German Translation

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