Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Herausgegeben von der Kommission Mamma (vertreten durch: Wolfgang Janni)
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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Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer
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Levels of Evidence and Grades of Recommendation
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1) Options for Primary Prevention: Modifiable Lifestyle Factors
2) Breast Cancer Risk and Prevention
3) Early Detection and Diagnosis
4) Pathology
5) Prognostic and Predictive Factors
6) Lesions of Uncertain Malignant Potential (B3) – ADH, LIN, FEA, Papilloma, Radial Scar
7) Ductal Carcinoma in situ (DCIS)
8) Breast Cancer Surgery Oncological Aspects
9) Oncoplastic and Reconstructive Surgery
10) Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
11) Adjuvant Cytotoxic and Targeted Therapy
12) Neoadjuvant (Primary) Systemic Therapy
13) Adjuvant Radiotherapy
14) Therapy Side Effects
15) Supportive Care
16) Breast Cancer: Specific Situations
17) Breast Cancer Follow-Up
18) Loco-regional Recurrence
19) Endocrine and "Targeted" Therapy in Metastatic Breast Cancer
20) Chemotherapy with or without Targeted Drugs in Metastatic Breast Cancer
21) Osteo-oncology and Bone Health
22) Specific Sites of Metastases
23) CNS Metastases in Breast Cancer
24) Complementary Therapy & Survivorship
25) Gynecological Issues in Breast Cancer Patients
## Oxford Levels of Evidence (LOE)

<table>
<thead>
<tr>
<th>LOE</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review (with homogeneity) of randomised controlled trials</td>
<td>Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomised controlled trials (with narrow Confidence Interval)</td>
<td>Individual inception cohort study with ≥ 80% follow-up; clinical decision rule validated in a single population</td>
</tr>
<tr>
<td>1c</td>
<td>All or none</td>
<td>All or none case-series</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review (with homogeneity) of cohort studies</td>
<td>Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomised controlled trials</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low quality randomised controlled trials; e.g., &lt;80% follow-up)</td>
<td>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</td>
</tr>
<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; Research; Ecological studies</td>
<td>&quot;Outcomes&quot; Research</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity) of case-control studies</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
<td>Case-series (and poor quality prognostic cohort studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
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## Oxford Grades of Recommendation (GR)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>consistent level 1 studies</td>
</tr>
<tr>
<td>B</td>
<td>consistent level 2 or 3 studies <em>or</em> extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>level 4 studies <em>or</em> extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>level 5 evidence <em>or</em> troublingly inconsistent or inconclusive studies of any level</td>
</tr>
</tbody>
</table>
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

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

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>D &amp; C</td>
<td>Dilatation and curettage</td>
</tr>
<tr>
<td>D / Carbo</td>
<td>Docetaxel / carboplatin</td>
</tr>
<tr>
<td>DAC</td>
<td>Docetaxel / doxorubicin / cyclophosphamide</td>
</tr>
<tr>
<td>DARB</td>
<td>Darbepoetin</td>
</tr>
<tr>
<td>DC</td>
<td>Docetaxel / cyclophosphamide</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>dd</td>
<td>Dose-dense</td>
</tr>
<tr>
<td>DepoCyt®</td>
<td>Liposomal cytarabine, liposomal ara-C</td>
</tr>
<tr>
<td>DFI</td>
<td>Disease-free interval</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease-free survival</td>
</tr>
<tr>
<td>DI</td>
<td>Dose intensity</td>
</tr>
<tr>
<td>DIEP-flap</td>
<td>Deep inferior epigastric perforator flap</td>
</tr>
<tr>
<td>Doc + Cap</td>
<td>Docetaxel + capecitabine</td>
</tr>
<tr>
<td>DOX, Doxo</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>E2, E₂</td>
<td>Estradiol</td>
</tr>
<tr>
<td>EBCTCG</td>
<td>Early Breast Cancer Trialists’ Collaborative Group</td>
</tr>
<tr>
<td>EC</td>
<td>Epirubicin / cyclophosphamide</td>
</tr>
<tr>
<td>ECD</td>
<td>Extracellular-domain</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear-nose-throat (otorhinolaryngologic)</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>Epi</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoetin</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen receptor</td>
</tr>
<tr>
<td>ErbB2</td>
<td>v-Erb-B2-erythroblastic leukemia viral oncogene homolog 2 (NEU)</td>
</tr>
<tr>
<td>ESF</td>
<td>Erythropoiesis-stimulating factor</td>
</tr>
<tr>
<td>ETC</td>
<td>Epirubicin / paclitaxel / cyclophosphamide (dose-dense chemotherapy)</td>
</tr>
<tr>
<td>EWGBSP</td>
<td>European Working Group for Breast Screening Pathology</td>
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### Abbreviations – IV

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

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

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

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No microscopic tumor residual</td>
</tr>
<tr>
<td>RAD</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>rand. Pat.</td>
<td>Patients randomized</td>
</tr>
<tr>
<td>RCT</td>
<td>Radiochemotherapy</td>
</tr>
<tr>
<td>Rec pos</td>
<td>Receptor positive</td>
</tr>
<tr>
<td>reg. CT + OP</td>
<td>Regional chemotherapy and operation</td>
</tr>
<tr>
<td>Rel. Risk</td>
<td>Relative risk</td>
</tr>
<tr>
<td>Reop</td>
<td>Re-operation</td>
</tr>
<tr>
<td>resp.</td>
<td>Respectively</td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency ablation</td>
</tr>
<tr>
<td>RFS</td>
<td>Recurrence-free survival</td>
</tr>
<tr>
<td>RPA</td>
<td>Recursive partitioning analysis</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase – polymerase chain reaction</td>
</tr>
<tr>
<td>S3</td>
<td>Highest level of evidence based guidelines according the Delphi-technique</td>
</tr>
<tr>
<td>SABCS</td>
<td>San Antonio Breast Cancer Symposium</td>
</tr>
<tr>
<td>Scottish CTPG and ICRF Breast Unit</td>
<td>Scottish Cancer Trials Breast Group and Imperial Cancer Research Foundation</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SERD</td>
<td>Selective estrogen receptor down-regulator</td>
</tr>
<tr>
<td>SERM</td>
<td>Selective estrogen receptor modulator</td>
</tr>
<tr>
<td>SF</td>
<td>Shortening fraction</td>
</tr>
<tr>
<td>SGAP-flap</td>
<td>Superior gluteal artery perforator-flap</td>
</tr>
<tr>
<td>signals/nucl.</td>
<td>Signals per nucleus</td>
</tr>
<tr>
<td>SIRT</td>
<td>Selective internal radiation therapy</td>
</tr>
<tr>
<td>SN</td>
<td>Sentinel lymph node</td>
</tr>
<tr>
<td>SNB-</td>
<td>Sentinel lymph node negative (not tumor infiltrated)</td>
</tr>
<tr>
<td>SNE, SLNE</td>
<td>Sentinel lymph node excision</td>
</tr>
<tr>
<td>Solitary Meta.</td>
<td>Solitary metastasis</td>
</tr>
<tr>
<td>Sonogr.</td>
<td>Sonography</td>
</tr>
<tr>
<td>SPF</td>
<td>S-phase fraction</td>
</tr>
<tr>
<td>SSM</td>
<td>Skin-sparing mastectomy</td>
</tr>
<tr>
<td>supra-/infraclav</td>
<td>Supraclavicular, infraclavicular</td>
</tr>
<tr>
<td>SWE</td>
<td>Sweden</td>
</tr>
</tbody>
</table>
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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- In order to minimize potential bias within the statements we followed the pre-defined rules:
  - These guidelines are strictly based on available evidence from the scientific literature.
  - The chapters of each edition were prepared by annually alternating teams of authors.
  - Each statement and the correspondent AGO-recommendations were thoroughly discussed within the entire group and accepted by majority decisions.
  - Each member of the editing committee is required to submit a written declaration of his/her conflicts of interests to an elected internal COI committee on an annual basis.
  - Members who do not submit a COI declaration may not participate in the guideline preparation.
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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)
Options for Primary Prevention: Modifiable Lifestyle Factors
Prevention

- **Version 2011:**
  Gerber / Thomssen

- **Versions 2012–16:**
  Dall / Diel / Gerber / Maass / Mundhenke

- **Version 2017:**
  Mundhenke / von Minckwitz
Non-modifiable Risk Factors for Breast Cancer

- Older age
- Genetic risk factors
- Family cancer history
- Personal history of breast lesions
  - Non-proliferative lesions
  - Proliferative lesions w/o atypia
  - High risk lesions (ADH, LIN)
  - Breast cancer (DCIS, InvBC)
- Breast density
- Chest irradiation
- Lifetime number of menstrual cycles
  - Early menarche, late menopause, mat. pregnancy factors (e.g. preeclampsia (risk reduction), gestational diabetes (risk increase))

Reproductive risk factors

- Lower number of births or no pregnancy
- Higher age at first full term delivery
Modifiable Risk Factors for Breast Cancer

- Less breast feeding
- BMI < 18.5 and > 25 and especially > 40 (obesity)
- Diabetes mellitus Type II
- Food content
- Steroid hormone therapy
  - Recent oral contraceptive use
  - Hormone therapy in postmenopausal women
- Alcohol intake
- Smoking
- Light exposure at night (night shifts)
- Low physical activity
- Toxic agents in fetal and early childhood development (DES, polyfluoroalkyls)
  - So far, there is no evidence for a correlation between aluminium containing antiperspirants and breast cancer
  - So far, there is no evidence for Glyphosate herbicide use and breast cancer
High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors

population attributable fractions (PAFs) of modifiable risk factors

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

**Results:** retrospective cohort study (Netherlands Cancer Registry)

2000: subpopulations of obese women, inactive women, alcohol drinkers, smokers etc.  
2010: breast cancer incidence as compared to background incidence in these subgroups

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

8.8% for obesity  
6.6% for alcohol  
5.5% for physical inactivity  
3.2% for low fibre intake  
4.6% for smoking

van Germert et al., Int J Cancer 2015; 152: 155-162
Secondary Prevention, Lifestyle and TNBC Subgroup

TNBC subgroup:

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

- factor: risk of recurrence
- phys. activity: HR 0.58 (0.39-0.86)
- BMI: no differences

Bao et al., Epidemiology 2015, 26:909-16
## Secondary Prevention, Lifestyle and ER-positive Subgroup

### ER-positive subgroup:

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

<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No weight gain</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;10% weight gain</td>
<td>1.24 (1.00-1.53)</td>
</tr>
<tr>
<td>BMI 30-34.99</td>
<td>1.40 (1.05-1.86)</td>
</tr>
<tr>
<td>BMI &gt;35</td>
<td>1.41 (1.02-1.62)</td>
</tr>
<tr>
<td>No alcohol</td>
<td>1.00</td>
</tr>
<tr>
<td>Daily alcohol</td>
<td>1.28 (1.091-1.62)</td>
</tr>
<tr>
<td>Phys. activity</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 17.4 MET-h/wk</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td>&gt; 17.4 MET-h/wk</td>
<td>0.71 (0.61-0.82)</td>
</tr>
</tbody>
</table>

Nechuta et al., Int J Cancer, DOI 10.1002 (Epub ahead of print)
Prevention by Changing Pregnancy Related Factors

- Any full term pregnancy
- Number of pregnancies
- First full term pregnancy before age of 30 years
- Breast feeding (protective if total breast feeding time exceeds 1.5–2 years)

Oxford / AGO
LoE / GR

2b B
2b B
2b B
3a B
Prevention by Changing Lifestyle Factors: Body Mass Index / Diet

- Maintaining normal weight (BMI at 18.5 – 25 kg/m²)
  - Premenopausal
  - Postmenopausal

- Prevention/Screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)

Oxford / AGO LoE / GR

2a B ++
3a B ++
2a B ++
2b B ++
## Prevention by Changing Lifestyle Factors: Diet

<table>
<thead>
<tr>
<th>Preference of a balanced diet*</th>
<th>2b</th>
<th>B</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat reduced food (unsaturated &gt; saturated fatty acids)</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Reduced consumption of red meat</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Supplementation of vitamins, minerals, tracer elements</td>
<td>2a</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin D substitution for prevention</td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Vegetables / fruits</td>
<td>2a</td>
<td>B</td>
<td>+/-**</td>
</tr>
<tr>
<td>Phytoestrogens / soya</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Fiber containing food</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Vegetarian diet (no risk reduction)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Vegan diet (no significant risk reduction)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* As recommended by German Society of Nutrition (DGE)
* **Recommended as a part of healthy nutrition
Prevention by Modifying Lifestyle Risk Factors: Alcohol

- Reduction of alcohol intake reduces risk of breast cancer

Particularly for
- ER+/PgR+ tumors
- Invasive lobular tumors

Oxford / AGO
LoE / GR

2b B

2b B

2b B
Prevention by Modifying Lifestyle Risk Factors: Smoking

- Never smoking reduces risk of breast cancer (~ 15-24% reduction of lifetime risk)

- Young women smoking have a 60% increased risk of bc, when smoking > 10 years before the first childbirth (vs. never smokers)
Prevention by Modifying Lifestyle Risk Factors: Physical Activity

- Physical exercise
  (Metabolic equivalents to 3–5 hrs moderate pace walking per week)
Prevention by Modifying Lifestyle Risk Factors:
Hormone Therapy in Postmenopausal Women

Avoiding hormonal therapy in postmenopausal women

- Avoiding estrogen / progestin combinations
  
- Avoiding estrogens only
  (no increasing risk for breast cancer by using estrogens alone, but increasing risk for endometrial cancer)
# Prevention

## Hormones in Postmenopausal Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MC-RR (95% CI)</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHI</strong></td>
<td>~ 27 000</td>
<td>1.3 (1.0-1.6)</td>
<td>1.3 (1.1-1.6) coronaric events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.4 (1.1-1.9) insults</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1 (1.4-3.3) pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1 (1.5-2.9) deep vein thrombosis</td>
</tr>
<tr>
<td><strong>HERS</strong></td>
<td>2763</td>
<td>1.2 (0.95-1.5)</td>
<td>med. age 67 J no secondary prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>side effects as compared to WHI + cholcystectomy</td>
</tr>
<tr>
<td><strong>Million Women</strong></td>
<td>1.084 110</td>
<td>1.66 (1.6-1.8)</td>
<td>EPC &gt; E mode of applic. not relevant duration &gt; 5 yrs.</td>
</tr>
<tr>
<td></td>
<td>~ 50% HRT</td>
<td></td>
<td>Tibolon RR 1.45 (1.2-1.7)</td>
</tr>
<tr>
<td></td>
<td>4.1 J follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPIC</strong></td>
<td>1.153 747</td>
<td>1.4 (1.2-1.6)</td>
<td>E-Mono EPC &gt; E</td>
</tr>
<tr>
<td></td>
<td>person-years</td>
<td>1.8 (1.4-2.2)</td>
<td>side effects as compared to WHI +</td>
</tr>
<tr>
<td><strong>Metaanalyse</strong></td>
<td>16 Studien</td>
<td>1.21-1.40</td>
<td></td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MC-RR (95% CI)</th>
<th>Further statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAR-study (NSW)</td>
<td>1236 BC cases</td>
<td>2.09 (1.57-2.78)</td>
<td>current user</td>
</tr>
<tr>
<td>Case-Control-Study, retrospect. Australia</td>
<td></td>
<td>1.03 (0.82-1.28)</td>
<td>past user</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.62 (1.56-4.38)</td>
<td>E/P combination</td>
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<tr>
<td></td>
<td></td>
<td>1.80 (1.21-2.68)</td>
<td>E only</td>
</tr>
</tbody>
</table>

**Salagame et al., Int J Cancer 2015. DOI 10.1002 Epub ahead of print**
Prevention by Modifying Lifestyle Risk Factors: Oral Contraception (OC)

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

Oxford LoE

1a

1a(−)
Options for Primary Prevention: Modifiable Lifestyle Factors (2/17)

Further information and references:

Screened data bases:

Screened guidelines:
ASCO (American Association of Clinical Oncology, Practice Guidelines, 2015)
CMA (Canadian Medical Association , 2015): http://www.cmaj.ca/cgi/content/full/158/3/DC1
NCCN (National Comprehensive Cancer Network , 2015):
Non Modifiable Risk Factors for Breast Cancer (3/17)

No further information

References:

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

No further information

References:

5. Nechuta et al., Int J Cancer, DOI 10.1002 (Epub ahead of print)
6. Bao et al., Epidemiology 2015, 26:909-16
High Proportion of Postmenopausal Breast Cancer Attributable to Lifestyle Factors (5/17)

No further information

No references
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:

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

No further information

References:

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

*No further information*

**References:**

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

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

7. Manson JE: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68.
9. Chlebowski et al., Climacteric 2015, 18:336-8
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:

Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

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

Version 2017:
Schmutzler / Fasching
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
Checklist according to Public Health Insurance Policies (German GKV)*

---

<table>
<thead>
<tr>
<th>A. Patientin oder Patient und deren Eltern/Geschwister/Kinder</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
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<td>3</td>
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<td>3</td>
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<tr>
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<tr>
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<td>1</td>
<td>2</td>
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Summe Patientin und deren Eltern/Geschwister/Kinder: A

<table>
<thead>
<tr>
<th>B. Weitere mütterliche Linie</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
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<td>2</td>
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<td>1</td>
<td>3</td>
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</tr>
<tr>
<td>eines Mammakarzinoms bei einem angehörenden Mann</td>
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<td>2</td>
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Summe weitere mütterliche Linie: B

<table>
<thead>
<tr>
<th>C. weitere väterliche Linie</th>
<th>Anzahl</th>
<th>Gewichtung</th>
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<td>eines Mammarkarzinoms bei einer Angestellten vor dem 36. LI.</td>
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<td>3</td>
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</tr>
<tr>
<td>eines Mammakarzinoms bei einem angehörenden Mann</td>
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<td>2</td>
<td></td>
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Summe weitere väterliche Linie: C

<table>
<thead>
<tr>
<th>D. Der höhere Wert aus B und C</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

E. Summe aus A und D = Risiko-Score: A+D

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*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](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

- **high risk genes (OR >5.0)**
  - (BRCA1/2, PALB2?)

- **moderately penetrant risk genes (OR 1.5 - 5.0)**
  - (RAD51C, ATM, BRIP1, CDH1, CHEK2, NBN, PTEN....)

- **low risk variants / modifiers (OR/HR <1.5)**
  - (FGFR2, TOX3, 2q35, 11q15, SLC4A7, 5p12, MAP3K1....)

**Contribution of known genes to familial aggregation of breast cancer**

- **BRCA1**
- **BRCA2**
- **TP53**
- **PTEN**
- **ATM**
- **CHEK2, BRIP1, PALB2**

- **Other genes familial risk factors**
- **79 common SNPs**
Breast Cancer Risk Genes with a High Lifetime Risk

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

- BRCA1, BRCA2
- PALB2
- ATM**
- CHEK2**

<table>
<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
<th>2a</th>
<th>A</th>
<th>++</th>
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<tr>
<td></td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td></td>
<td>3a</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene Alteration</th>
<th>Lifetime Risk BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li Fraumeni</td>
<td>p53</td>
<td>~ 50 %&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>~ 25 %&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td>CDH1</td>
<td>~40-50 % (lobular)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/ LKB1</td>
<td>~45-50 %&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: ~20 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervix: ~10 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterus: ~10 %</td>
</tr>
<tr>
<td>Lynch</td>
<td>mismatch repair MLH1, MSH2, MSH6, PMS2</td>
<td>up to twofold increased risk compared to general population&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial: ~25-60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: up to 25 %</td>
</tr>
<tr>
<td>Ataxia telangiectasia (AT-Syndrome)</td>
<td>ATM</td>
<td>20-40 %&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Franconi Anämie</td>
<td>RAD51C / D PALB2</td>
<td>Ovary: ~ 10 %&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 30 %&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nijmegen-Breakage Syndrome</td>
<td>NBN</td>
<td>20-30 %&lt;sup&gt;10,11&lt;/sup&gt; for slavic founder mutation 657del5</td>
</tr>
</tbody>
</table>

**Recommendation:** genetic counseling: GCP
Clinically not validated Breast Cancer Gene Panels for Risk Prediction

**BROCA 40 gene panel**
- APC
- ATM
- BAP1
- BRCA1
- BRCA2
- CDK4
- CDKN2A
- CHEK1
- CHEK2
- EPCAM
- FAM175A
- GALNT12
- GEN1
- GREM1
- HOXB13
- MLH1
- MRE11A
- MSH2
- MSH6
- NBN
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

**AMBRY Genetics BreastNext**
- ATM
- BARD1
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- EPCAM
- FANCA
- FANCC
- FANC D
- FANCE
- FANC F
- FANC G
- MEN1
- MLH1
- MRE11A
- MSH2
- MSH3
- MSH6
- NBN
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

**CEGAT CAN02: Brust- und Ovarialkarzinom (30 genes)**
- ATM
- BARD1
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- EPCAM
- FANCA
- FANCC
- FANC D
- FANCE
- FANC F
- FANC G
- HRAS
- KIT
- MAX
- MRE11A
- MLH1
- MS H2
- MSH6
- MUTYH
- NBN
- NF1
- NF2
- NSD1
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

**TruSight™ Cancer (Illumina)**
- AIP
- ALK
- ATM
- BARD1
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- EPCAM
- FANCA
- FANCC
- FANC D
- FANCE
- FANC F
- FANC G
- MEN1
- MLH1
- MRE11A
- MSH2
- MSH3
- MSH6
- NBN
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

**CENTOGENE BC/OC panel**
- ATM
- BARD1
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- MRE11A
- MLH1
- MSH2
- MSH6
- MUTYH
- NBN
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

**MYRIAD myRISK Panel**
- ATM
- BARD1
- BRCA1
- BRCA2
- BRIP1
- CDH1
- CHEK2
- MRE11A
- MLH1
- MSH2
- MSH6
- MUTYH
- NBN
- PALB2
- PTEN
- RAD50
- RAD51C
- STK11
- TP53

Further Information
References

www.ago-online.de
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
Genotype determines not only disease penetrance but phenotype and clinical disease course.
Genetically Defined Subtypes are Distinct Tumor Entities

- Distinct genetic subtypes of breast cancer may show distinct clinical features. Prior to the offer of prophylactic measures the following questions should be addressed:
  - Disease penetrance?
  - Typical histopathological features?
  - Sensitivity to current screening modalities?
  - Better survival of early detected tumors?
  - Natural disease course?
  - Response to anti-tumor therapy?

Genotype-phenotype-correlations must be employed
VUS: Problems and Questions

- **“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-occurrence analysis, large case / control studies
- In silico prediction tools (PolyPhen2, SIFT) are not adequate for clinical decision making
- Classification of sequence variants should be performed according to the IARC classification system
- Clinical interpretation and decision making depending on the IARC classification system is not standardized yet
Variant classification proposed by IARC (Plon et al., Human Mutation, 2008)

Only class 4 and 5 variants are considered clinically relevant.
Classification of IARC Class 3 Variants

Requires additional information and analyses, e.g.
- Co-occurrence data from large data banks
- Segregation analysis
- Functional analysis etc.

To be accumulated by large study groups such as ENIGMA

Improvement of IARC class 3 classification in the German population by GC-HBOC
Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing*

- The risk collective is clearly defined by risk criteria
- The positive predictive value of risk criteria with respect to the identification of the genetic risk factor is known
- The cut-off values for genetic testing evolved through a transparent consensus process
- The genetic test is valid and reliable
- A spectrum bias is excluded or defined
- A clinical prevention strategy exists that leads to early detection or prevention and mortality reduction of the genetically defined subset of the disease

Acc. to the position paper on risk-adjusted early detection of cancer of the German National Cancer Plan developed under the Federal Ministry of Health
http://www.bmg.bund.de/themen/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/querschnittsthema-risiko-adaptierte-krebsfrueherkennung.html
Current Clinical Impact of non-BRCA1/2 Breast Cancer Risk (NBBC) Genes

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

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

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

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

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

---

Oxford / AGO LoE / GR
3b B +/−
3b D −
5 D +
Non Directive Counseling for the Uptake of Preventive Measures

- 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
Definition of Women at Moderate to High Risk

- Deleterious mutation in the BRCA1, BRCA2
- High risk (mutation probability of $\geq 10\%$ OR heterozygous risk of $\geq 20\%$ OR remaining life time risk of $\geq 30\%$ acc. to a validated standard risk prediction models*)
- Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)

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

Oxford / AGO
LoE / GR

1a  A  ++
2b  B  +
2a  B  ++
Surveillance Program for Female Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC*

Multimodal intensive surveillance program lifelong

For the detection of early stage breast cancers

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

Multimodal intensive surveillance program lifelong

For the detection of early stage breast cancers

- 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)

Oxford / AGO LoE / GR

2a B ++

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

Currently no specific surveillance is recommended

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

Oxford / AGO LoE / GR

*Follow up care / surveillance should be performed within structured and quality assured programmes, that capture performance and outcome of early detection / screening measures
Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

- Increased risk of breast cancer after chest irradiation because of Hodgkin lymphoma in childhood (8-18 years)
- Increased risk of breast or ovarian cancer in women from BRCA1/2 negative families at risk that is, however, lower than in women from BRCA1/2 positive families
- Referral to centres of the GC-HBOC or cooperating centres for the evaluation of structured surveillance and follow-up
Surgical Prevention

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

Oxford / AGO LoE / GR

2a B +*
Surgical Prevention for Healthy Female BRCA1/2 Mutation Carriers

- **Risk-reducing bilateral salpingo-oophorectomy (RR-BSO, PBSO) around 40 years of age**
  - reduces OvCa incidence and mortality
  - reduces BrCa incidence and mortality
  - reduces overall mortality

- **Contralateral mastectomy (RR-BM, PBM)**
  - reduces BrCa incidence and mortality

RR-BSO is performed after completion of family planning
RR-BM revealed a high incidence of premalignant lesions

*Study participation recommended*
Risk-reducing Interventions for BRCA1/2 Female Mutation Carriers Affected by Breast Cancer

- **Bilateral salpingo-oophorectomy (RR-BSO)**
  reduces OvCa incidence and mortality
  reduces BrCa mortality
  reduces overall mortality
  (contradictory results for reduction of cl BrCa incidence)

- **Contralateral mastectomy + (RR-BM)**
  reduces cl BrCa incidence and mortality

- **Tamoxifen (reduces cl BrCa incidence)**

- **Indication for PBM should consider age at onset of first breast cancer and the affected gene**
  + Overall prognosis has to be considered

*Study participation recommended*
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.


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

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

Limited prospective cohort studies with short follow-up time

- 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 B +

- PARP inhibitor in breast cancer 2b D +/-

+ Overall prognosis has to be considered

*Study participation recommended
Medical Prevention for Women at Increased Risk

- Tamoxifen for women > 35 years
  Reduction of invasive BrCA, DCIS, and LN

- Raloxifen for postmenopausal women
  Reduction of invasive BrCa only

- AI for postmenopausal women

Significant risk reduction was seen for anastrozole for ovarian and endometrial cancer, as well as skin, colorectal, hematologic, thyroid and urinary tract cancers.

Chemopreventive regimes should only be offered after individual and comprehensive counseling. The net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1.66% in 5 years)
Risk Reduction for Ipsi- and Contralateral Breast Cancer

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

- Tamoxifen*
  - Oxford / AGO LoE / GR: 1a A +
- Aromatase inhibitors*
  - Oxford / AGO LoE / GR: 1a A +
- Suppression of ovarian function* + Tamoxifen
  - Oxford / AGO LoE / GR: 1b B +

*Only proven for ER/PgR-positive primary sporadic BrCa
Cooperation of Certified Breast Cancer (BC) Centres (Ctr) with Familial BC Ctr of the GC-HBOC*

Check list (inclusion criteria)
Counselling for diagnostic genetic testing

Certified BC Ctr

Genetic testing

Communication, Exchange, Advice

Familial BC Ctr

Counselling: Indication for surveillance and/or prophylactic surgery

Prophylactic surgery

Stratified therapy

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

Checklist according to Public Health Insurance Policies (German GKV)* (5/31)

No further information

No references
No further information

References:

Breast Cancer Risk Genes with a High Lifetime Risk (7/31)

No further information

References:

Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (8/31)

No further information

References:


Clinically not Validated Breast Cancer Gene Panels for Risk Prediction (9/31)

No further information

References:

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:

**Genetically defined Subtypes are distinct Tumor Entities (12/31)**

*No further information:*

**References:**

VUS: Problems and Questions (13/31)

No further information

References:

Variant Classification proposed by IARC (14/31)

No further information

References:

Classification of IARC Class 3 Variants (15/31)

No further information

References:

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing* (16/31)

No further information

References:

Current Clinical Impact on non-BRCA1/2 Breast Cancer risk Genes (17/31)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (18/31)

No further information

No references
Definition of Women at Moderate to High Risk (19/31)

No further information

References:


Surveillance Program for Female Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC* (20/31)

No further information

References:

Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer cc. to GC-HBOC* (21/31)

No further information

References:

Surveillance for Male Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC* (22/31)

No further information

References:

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

(23/31)

*No further information*

**References:**


Surgical Prevention (24/31)

No further information

References:

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

Further information:

Prophylactic bilateral salpingo-oophorectomy (PBSO) reduces the risk for ovarian cancer in BRCA1/2 mutation carriers to >95% and the risk for breast cancer to 50% (Kauff et al. NEJM 2002, Rebbeck et al. NEJM 2002). Short term HRT does not negate the protective effect of PBSO on subsequent breast cancer risk (Rebbeck et al. 2005). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow up (Casey et al. Gynecol Oncol 2005). Moreover, PBSO improves overall survival of mutation carriers (Domchek et al. The Lancet 2006). These studies support the current strategy of the German consortium to recommend PBSO in mutation carriers after completion of childbearing around the age of 40.

Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.

For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).

The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be preceded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)
References:

Risk-reducing Interventions for Female BRCA1/2 Female Mutation Carriers Affected by Breast Cancer (26/31)

No further information

References:


Improved Overall Survival After Contralateral Risk-reducing Mastectomy in BRCA1/2 Mutation Carriers (27/31)

No further information

References:

Therapy of BRCA1/2-associated Breast Cancer (28/31)

*No further information*

*No references*
Medical Prevention for Women at Increased risk (29/31)

No further information

References:

Risk Reduction for Ipsi- and Contralateral Breast Cancer (30/31)

No further information:

References:

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

No further information

No references
Early Detection and Diagnosis
Early Detection and Diagnosis

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

- **Version 2017:**
  Albert / Müller-Schimpfle
# Early Detection Mammography

<table>
<thead>
<tr>
<th>Age</th>
<th>Interval</th>
<th>LOE / GR</th>
<th>Oxford</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>na</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40–49</td>
<td>12–24</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>50–69*</td>
<td>24</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>70–74</td>
<td>24</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>&gt;75**</td>
<td>24</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

*National Mammography-Screening-Program
**health status + life expectancy more than 10 years
## Breast Cancer Mortality Reduction

### Meta-Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>RR  95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent UK Panel, 2012</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td>13-year metaanalysis</td>
<td></td>
</tr>
<tr>
<td>Cochrane Review, 2011</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td></td>
</tr>
<tr>
<td>As above, but excluding women &lt;50 years</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td>US Task Force, 2009</td>
<td></td>
</tr>
<tr>
<td>Women 50–59 years</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>Women 60–69 years</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td>Estimates weighted average</td>
<td>0.81</td>
</tr>
<tr>
<td>Canadian Task Force, 2011</td>
<td></td>
</tr>
<tr>
<td>Women aged 50–69 years</td>
<td>0.79 (0.68–0.90)</td>
</tr>
<tr>
<td>Duffy et al., 2012</td>
<td></td>
</tr>
<tr>
<td>Review of all trials and age groups</td>
<td>0.79 (0.73–0.86)</td>
</tr>
</tbody>
</table>
## Breast Cancer Mortality Reduction

### Meta-Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broeders et al</td>
<td>Screening Mx</td>
<td>0.46 (0.4 – 0.54)</td>
</tr>
<tr>
<td></td>
<td>Corr. for self selection</td>
<td>0.52 (0.42-0.65)</td>
</tr>
<tr>
<td></td>
<td>Invited for screening</td>
<td>0.69 (0.57-0.83)</td>
</tr>
<tr>
<td><strong>Incidence-based Mortality Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broeders et al</td>
<td>Screening Mx</td>
<td>0.62 (0.56-0.69)</td>
</tr>
<tr>
<td></td>
<td>Invited to screening</td>
<td>0.75 (0.69-0.81)</td>
</tr>
<tr>
<td><strong>Randomized Clinical Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gotsche and Jorgenson</td>
<td>Screening Mx</td>
<td>0.81 (0.74-0.87)</td>
</tr>
</tbody>
</table>
# Breast Cancer Mortality Reduction

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>NNS</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>40 - 49</td>
<td>1770</td>
<td>753</td>
</tr>
<tr>
<td>50 - 59</td>
<td>1087</td>
<td>462</td>
</tr>
<tr>
<td>60 - 69</td>
<td>835</td>
<td>355</td>
</tr>
</tbody>
</table>

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

Oeffinger KC et al  JAMA 2015;314
Breast Cancer Screening
ACS Guideline Update 2015

American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (e.g., 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 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.
# Breast-Cancer Screening: Viewpoint of the IARC Working Group

<table>
<thead>
<tr>
<th>Method</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces breast-cancer mortality in women 50-69 yr of age</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 70-74 yr of age</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 40-44 yr of age</td>
<td>Limited</td>
</tr>
<tr>
<td>Reduces breast-cancer mortality in women 45-49 yr of age</td>
<td>Limited</td>
</tr>
<tr>
<td>Detects breast cancer that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)</td>
<td>Sufficient</td>
</tr>
<tr>
<td>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</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Produces short-term negative psychological consequences when the result is false positive</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Has a net benefit for women 50-69 yr of age who are invited to attend organized mammographic screening programs</td>
<td>Sufficient</td>
</tr>
</tbody>
</table>
Mammography-Screening
Women 40–49 Years

RR (invited women)  
40–44 J  
45–49 J  
Participants

0.74 (95%CI 0.66-0.83)  
0.83 (95%CI 0.67-1.00)  
0.68 (95%CI 0.59-0.78)  
0.71 (95%CI 0.62-0.80)

NNS  
1252 (95%CI 958-1915)

(1 live saved / 10 years screening)

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

- Screening-Breast Sonography
  - Automated 3D-Sonography

As an adjunct:
- Dense mammogram
  (density 3–4/composition C-D)
  - Elevated risk
- Mammographic lesion
- Second-look US (MRI-only detected lesions)
Early Detection
Clinical Examination

As stand alone procedure

- Self-examination
  1a A -*
- Clinical breast examination (CBE)
  3b C -*
  by health professionals

- CBE because of mammo/sonographic lesion
  5 D ++

CBE in combination with imaging

BCP ++

* May increase breast awareness
### Assessment of Breast Symptoms or Lesions

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / LOE</th>
<th>AGO GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>3b B</td>
<td>++</td>
</tr>
<tr>
<td>Mammography</td>
<td>1b A</td>
<td>++</td>
</tr>
<tr>
<td>Additional Tomosynthesis (vs spot compression)</td>
<td>3b B</td>
<td>+</td>
</tr>
<tr>
<td>Sonography</td>
<td>2b B</td>
<td>++</td>
</tr>
<tr>
<td>Elastography (shear-wave)</td>
<td>2a B</td>
<td>+</td>
</tr>
<tr>
<td>Automated 3D-sonography</td>
<td>3b B</td>
<td>+/-</td>
</tr>
<tr>
<td>MRI*</td>
<td>2b B</td>
<td>+/-</td>
</tr>
<tr>
<td>Minimally invasive biopsy</td>
<td>1c A</td>
<td>++</td>
</tr>
</tbody>
</table>

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

- Clinical examination
  - Mammography
  - Mammography + Tomosyntheses + Sonography added MRI
  - Sonography
    - Axilla + FNP/CNB
  - MRI *
  - Minimally invasive biopsy**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford</th>
<th>LOE</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Mammography + Tomosyntheses + Sonography</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mammography + Tomosyntheses + Sonography +</td>
<td>3b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Axilla + FNP/CNB</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>MRI</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Minimally invasive biopsy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>

* 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
MRI: Preoperative Staging

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

MRI: Preoperative Staging in Lobular Invasive Breast Cancer

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

MRI Screening (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

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

Prospective study results for MRI screening in women with high familiar risk (H) and mutation carriers (M)
## MRI Screening (High-risk) Problems

<table>
<thead>
<tr>
<th>MRI in addition to mammography</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive MRI</td>
<td>3.43–4.86</td>
</tr>
<tr>
<td>Benign biopsies</td>
<td>1.22–9.50</td>
</tr>
<tr>
<td>Benign surgical biopsies</td>
<td>2</td>
</tr>
<tr>
<td>(MARIBS)</td>
<td></td>
</tr>
<tr>
<td>False-negative MRI (MRISC)</td>
<td>22%</td>
</tr>
</tbody>
</table>
MRI and DCIS

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

„Negative breast MRI findings should not be considered a sure marker of benignancy.“
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 impairment and better quality of life. Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false positives, false negatives, overdiagnosis and overtreatment. (IARC 2016, European Commission 2016, ACS 2015, USPSTF 2016)

Meta-analysis and reviews from randomised trials:
Conclusion of the meta-analysis of the Independent UK Panel on Breast Cancer Screening: “Considering the internal bias in the trials, which were done a long time ago, the relative risk reduction in breast cancer mortality from invitation to mammography screening is estimated to be 20%.”

Data from observational studies and registries:
The EUROSCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: “the best “European” estimate of breast cancer reduction is 25-31% for women invited for screening, and 38-48% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis”.

The population-based data from the United States (SEER-Cancer Statistics 1976 - 2009) showed a 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.
References:


24. Walter LC, Schonberg MA. Screening mammography in older women: a review. JAMA 2014;311(13):1336-1347

Breast Cancer Mortality Reduction (4/19)

No further information

References:

Breast Cancer Mortality Reduction (5/19)

No further information

References:

Breast Cancer Mortality Reduction (6/19)

No further information

References:

Breast Cancer Screening – ACS Guideline Update 2015 (7/19)

No further information

References

Breast Cancer Screening – Viewpoint of the IARC Working Group (8/19)

No further information

References:

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

Further information:

On the basis of randomized controlled trials there is evidence of a 26% mortality reduction. The only one especially designed for this age group (“Age-Trial”) achieved a mortality reduction of 17% for those invited and 24% for those participating. These results were not yet statistically significant (95% CI, 0.66-1.04)), because the follow-up time was too short for this young age group. Recently a significant reduction in breast cancer mortality in the first 10 years after diagnosis as noted in the intervention group compared with the control group (RR 0.75, CI 0.58-0.97), but not thereafter. The data have been underlined by study results of several service screening studies (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.”

References:

3. FH01 Collaborative Teams Mammographic surveillance in women younger than 50 years who have a family history of breast cancer: tumour characteristics and projected effect on mortality in the prospective, single-arm, FH01 study. Lancet Oncol 2010;11:1127-1134
10. Moss SM et al. Effect of mammographic screening from age 40 years on breast cancer mortality a 10 years follow-up: a randomised controlled trial. The Lancet 2006; 368: 2053 – 2060
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).

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

References:


ABUS/AVUS


US-Screening


Dense Breast


Elevated Risk


Recommendations International

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.

References:

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.
References:


Tomosynthesis


3. Cornford EJ1, Turnbull AE2, James JJ1, Tsang R1, Akram T2, Burrell HC1, Hamilton LJ1, Tennant SL1, Bagnall MJ2, Puri S2, Ball GR3, Chen Y4, Jones V5: Accuracy of GE digital breast tomosynthesis vs supplementary mammographic views for diagnosis of screen-detected soft-tissue breast lesions. Br J Radiol. 2016;89(1058):20150735


Elastography


Automated Breast Ultrasound (ABUS)


**Pretherapeutic Assessment of Lesion Extension and Staging (13/19)**

**Further information:**

Sonography corresponds better than mammography with the pathological tumour size of the invasive component of breast tumours. Mammography delineates the in situ component better if microcalcifications are present. In these cases magnification mammography is warranted. MRI is the most sensitive method for both invasive and non-invasive tumours, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment. A recent prospective study examined the accuracy of digital breast tomosynthesis (DBT) and magnetic resonance imaging (MRI) added to digital mammography (DM) and ultrasound (US) in the preoperative assessment of breast cancer. DBT had higher sensitivity than DM (90.7% vs. 85.2%). Combined DM and DBT with US yielded a 97.7% sensitivity; despite high sensitivity of MRI (98.8%), the addition of MRI to combined DM with DBT and US did not significantly improve sensitivity. Overall accuracy did not significantly differ between MRI and DM with DBT and US (92.3% vs. 93.7%). Breast density affected sensitivity of DM and DBT (statistically significant difference for DM), not MRI. The authors concluded that there is little gain in sensitivity and no gain in overall accuracy, by performing MRI for patients who have been evaluated with DM with DBT and US (Mariscotti G et al 2014).

Axillary ultrasound is recommended for pretherapeutic assessment to guide axillary surgery (Feng Y et al 2015). Elastography of lymph nodes might add prognostic information additional to that provided by conventional preoperative tumor assessment and staging. A general recommendation for the use of lymph node elastography cannot be given as data on quality assurance is lacking.

MRI for preoperative staging may be helpful in individual cases (high-risk women, multifocality/multicentricity demonstrated at conventional imaging and pathologically proven, invasive lobular cancer with inconclusive findings at conventional imaging), but considering the present evidence no general recommendation can be given for preoperative MRI in patients before breast conservation in both invasive and non-invasive cancer.

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

Combined DM + DBT + US + MRI


US-Axilla +FNA/CNB


Biopsie

2. Lourenco AP, Mainiero MB Incorporating imaging into the locoregional management of breast cancer. Semin Radiat Oncol 2016;26(1)

MRT

least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. Eur J Cancer. 2016 Jan;52:67-76.
MRI: Preoperative Staging (14/19)

No further information

References:

5. Sardanelli F. Overview of the role of preoperative breast MRI in the absence of evidence on patient outcomes. Breast 2010; 19: 3-6
MRI Preoperative Staging in Lobular Invasive Breast Cancer (15/19)

No further information

References:


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.

References:

MRI Screening (High Risk) Problems (18/19)

No further information

References


3. Saadatmand S, Obdeijn IM, Rutgers EJ, Oosterwijk JC, Tollenaar et al. Survival benefit in women with BRCA1 mutaion or familial risk in the MRI screening study (MRISC) Int J Cancer 2015; 137(7): 1729-1738

MRI and DCIS (19/19)

No further information

References:

Pathology
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
Preanalytics: Fixation

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

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Use of Fine Needle Aspiration Cytology*

- Nipple secretion
- Tumor
- Cyst
- Lymph node

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

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<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Routine workup in step sections (14G: 3 sections / 11G, 8G: 6–8 sections)</th>
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<td>Correlation with imaging (density, calcifications), use of B-classification</td>
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<td>Frozen section diagnosis on core biopsies</td>
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<td>Routine evaluation of ER/PgR and HER2 status</td>
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<td>Turn-around time &lt; 24 h (histology)</td>
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Workup: Breast-Conserving Specimens

- Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)  
- Systematic sampling, at least 1 tissue block every 1 cm  
- Inking of resection margins. Sampling of resection margins in all dimensions  
- Documentation after slicing using specimen radiography, photodocumentation or diagram

Oxford / AGO LoE / GR

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Workup: Mastectomy Specimens

- **Margins always to be sampled**
  - Skin close to tumor, at least 2 directions
  - Deep margin
  - Other margins, if close (< 1 cm)

- **Attention to soft tissue margins in skin sparing mastectomy**

- **Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region**

- **More extensive sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)**
# Workup: Sentinel Node Biopsy

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- **Full workup using step sections of \( \leq 500 \, \mu m \) on paraffin embedded tissue**
  - Oxford / LoE / GR: 5 D ++

- **Cytokeratin immunohistochemistry**
  - When suspicious, to detect micromet.
  - As a routine procedure
  - Oxford / LoE / GR: 5 D +/-

- **Frozen section (invasive Ca.)**
  - If clinical consequence
  - If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BCT)
  - Oxford / LoE / GR: 5 D +/

- **Imprint cytology instead of, or in addition to frozen section**
  - Oxford / LoE / GR: 3b C +/-

- **RT-PCR for epithelial genes**
  - OSNA
  - Oxford / LoE / GR: 3b B -
### Indications for Immediate Pathological Analysis Including Frozen Sections

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<td>Sentinel node biopsy for invasive cancer</td>
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<td>- If clinical consequence</td>
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<td>- If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)</td>
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<td>Closest margin of resection</td>
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<td>- If macroscopically &gt; 1 cm</td>
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<td>Lesions ≥ 1 cm, without core biopsy</td>
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<td>Non-palpable lesions or lesions &lt; 1 cm</td>
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<td>Asservation of fresh tissue (tumor banking)</td>
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Reporting: Histologic Tumor Type

- Histologic tumor typing according to WHO-Classification, (4th ed., 2012)
  - Partial special differentiation:
    > 50% NST component
    and < 50% special tumor type (minor component)
  - Mixed differentiation:
    > 50% special tumor type
    and < 50% NST component
    Example: mucinous breast cancer, mixed type
  - Pure types:
    > 90% special tumor type
    Examples: tubular or cribriform Ca.
Reporting: Grade of Malignancy

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

- Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results
  - Oxford LoE / AGO LoE / GR
  - 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 ++
Reporting: pTNM

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

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

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

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

- **pM**: pM1 indicates any non-regional disease, except 2nd primary contralaterally. Use of MX is not recommended.
Reporting: Margins of Resection and R-Classification

- Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm)  
  Oxford LoE / AGO GR  
  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)
**Reporting: Lymphovascular Invasion**

- **L1**: Lymphovascular invasion  
  **L0**: No lymphovascular invasion

- IHC for evaluation of lymphovascular invasion

- Differentiation of peritumoral and extensive lymphovascular invasion

- Reporting of venous invasion (V0/V1) optional, prognostic significance not established

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Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

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

Consider only lymphocytic infiltrate in tumor stroma and not at the invasion front

Do not consider central fibrosis and necrotic areas

Report average of lymphocytic infiltrate as percentage

Reporting: Evaluation after Neoadjuvant Chemotherapy

- Identification of tumor bed, otherwise ypTX
  
- Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma
  
- pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded

- Use of IHC to identify tumor residues
- Reporting of ypTN after therapy
- Repeat IHC for ER, PgR, and HER2

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Special Studies: ER-Testing by IHC

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
  - Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%, low pos. if ≥ 1%-9%)
  - Staining intensity of pos. tumor nuclei (0 - 3)
  - Allred Score (0 - 8), Remmele Score (0 - 12)
  - Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy

For therapeutic implications see chapter “Endocrine therapy”

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<td>Staining intensity of pos. tumor nuclei (0 - 3)</td>
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<td>Allred Score (0 - 8), Remmele Score (0 - 12)</td>
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Special Studies: PgR-Testing by IHC

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
  - 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 +
Additional Special Studies: Molecular Analysis of ER/PgR Status

- Evaluation of hormone receptors using validated gene expression test kits
  - Oxford / AGO
  - LoE / GR
  - 3b A +/-

- Evaluation of hormone receptor by RNA-sequencing
  - 5 D -

- Use of molecular receptor analysis for subtyping
  - 3b A +
Special Studies: HER2 Testing

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

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

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

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

- Validation of immunohistochemistry on core biopsies
False positive immunohistochemical labeling may occur in core biopsies. Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium. Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.

False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PgR positive, Tubular (at least 90% pure), Mucinous (at least 90% pure) Cribriform (at least 90% pure), Adenoid cystic carcinoma (90% pure)

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples.

Expected rate of HER2-overexpression: 15% HER2 positive
Additional Special Studies:
Molecular Analysis of HER2 Status

- Therapy decisions should be based on IHC and ISH only
- Evaluation of HER2 durch using validated gene expression test kits
- Evaluation of HER2-amplification by RNA-sequencing
- Use of molecular HER2-testing for subtyping

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>
Special Studies:
Evaluation of Ki-67 Score

<table>
<thead>
<tr>
<th>Oxford / LoE / GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>5    D</td>
<td>++</td>
</tr>
<tr>
<td>5    D</td>
<td>++</td>
</tr>
<tr>
<td>5    D</td>
<td>++</td>
</tr>
<tr>
<td>5    D</td>
<td>++</td>
</tr>
<tr>
<td>5    D</td>
<td>+</td>
</tr>
</tbody>
</table>

- Counting of tumor nuclei at the invasion front
- Consideration of weakly stained tumor nuclei
- Reporting of Ki-67 positive nuclei as percentage
- Establishing of laboratory standards and cut-off values
- Use of image analysis for objective Ki-67 evaluation
Intrinsic Breast Cancer Types
(Molecular and Immunohistochemical Definitions)

- 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)
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
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
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:


Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.1.2014
- Cochrane: 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

References:

Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 2008. 
General principles for Histopathologic Examination of Breast Cancer Specimens (3/30)

No further information

References

Preanalytics: Fixation (4/30)

No further information

References:

Antigen preservation


Retraction artifacts


Use of Fine Needle Aspiration Cytology (5/30)

No further information

References:

Workup: Macroscopy and Specimen Radiography (6/30)

No further information

References:

Clinical-pathological correlation diagnostics


Image documentation

Specimen radiography


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

No further information

**References:**

Statement: Routine workup in step sections


Statement: Correlation with imaging


Statement: Frozen section diagnosis on core biopsies

Statement: Routine evaluation of ER/PgR and HER-2 status


Statement: Turn-around time < 24h

Workup of Breast-Conserving Specimens (8/30)

No further information

References:


Workup of Mastectomy Specimens (9/30)

No further information

References:

Workup: Sentinel Node Biopsy (10/30)

No further information

References:

Statement: Evaluation of sentinel node biopsy:


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


Statement: Frozen section

Statement: Imprint cytology instead or in addition of frozen section


Statement: RT-PCR for epithelial genes

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

*No further information*

**References:**

**Statement: Sentinel node biopsy for invasive cancer**


**Statement: Closest margin of resection**

Statement: Lesions $\geq 1$ cm, without core biopsy


Statement: Non-palpable lesions or lesions < 1 cm

Reporting: Histologic Tumor Type (12/30)

No further information

References:

WHO-Classifikation

2. Lakhani SR, Ellis I, Schnitt S et al. (2012) WHO Classification of Tumours of the Breast. IARC Press, Lyon
Reporting: Grade of Malignancy (13/30)

No further information

References:

Grading

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

Grading of invasive lobular carcinoma

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

No further information

References:

Determination of tumor size


Multifocality


**Extensive intraductal component (EIC)**

Reporting: pTNM (15/30)

No further information

References:

TNM staging (7th ed.) according to UICC und AJCC


pT4b category: Involvement of the skin


pT4d category: Inflammatory breast cancer

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

*No further information*

**References:**

Pathological margin assessment


R-Classifikation

**Reporting: Lymphovascular invasion (17/30)**

*No further information*

**References:**

**Definition of L- and V-Classification**


**Detection of angioinvasion**

Prognostic significance of lymphovascular invasion

**Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL) (18/30)**

*No further information*

**References:**

Definition and impact of predominant lymphocytic infiltration

Reporting: Evaluation after Neoadjuvant Chemotherapy (19/30)

No further information

References:

Specimen processing after neoadjuvant chemotherapy


RCB-Score

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

No further information

References:

IHC-testing for ER-positivity


IHC Scores


Monoclonal Antibodies for ER-Testing

1. Cheang MC, Treaba DO, Speers CH, Olivotto IA, Bajdik CD, Chia SK, Goldstein LC, Gelmon KA, Huntsman D, Gilks CB, Nielsen TO, Gown AM.
2. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival.

Low ER+ Group (≥1%<10%)

3. Sanford AS et al. High Incidence of Germline BRCA Mutation in Patients with ER
Special studies: PgR-Testing by IHC (21/30)

No further information

References:

IHC-testing for PR-positivity

Prognostic significance


Aberrant Expression of ER in triple negative breast cancer


IHC Scores

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

No further information

**References:**

Clinical significance of mRNA expression of ESR-alpha, PgR and concordance with IHC results


Special studies: HER2 Testing (23/30)

No further information

References:

2. Chivukula M, Bhargava R, Brufsky A et al. (2008) Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. Mod Pathol 21:363-368
HER2 Testing on Core Biopsies (24/30)

No further information

No references
Additional Special studies: Molecular Analysis of HER2 Status (25/30)

No further information

References:

Clinical significance of mRNA expression of HER2 and concordance with IHC results


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

No further information

References:

Ki-67 Methods and Reproducibility

Impact of Ki-67 staining


Ki-67 Image Analysis


Intrinsic Breast Cancer Types (27/30)

No further information

No references
Quality assurance: Immunohistochemistry (28/30)

No further information

References:

Quality assurance: HER2-Status (29/30)

No further information

No references
Quality assurance: Reporting (30/30)

No further information

No references
Prognostic and Predictive Factors
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
“Low absolute risk implies low absolute benefit”

Quality Criteria

- Biological hypothesis
- Simple and reliable determination method, quality assurance (QA) of the test
- Prospectively planned statistical evaluation (primary goal)
- Validation of clinical significance according to
  - „Oxford Level of Evidence (LoE_{Ox2001})“ criteria and „Grades of Recommendation (GR)“
  - „Grades of Recommendation (GR)“ as well as modified LoE criteria for the use in archived specimen (LoE_{2009}) and category of tumor marker study (CTS)
- Clinical relevance for treatment decisions

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
## Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

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

# Revised Determination of Levels of Evidence using Elements of Tumor Marker Studies

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Category</th>
<th>Validation studies available</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>None required</td>
</tr>
<tr>
<td>I</td>
<td>B</td>
<td>One or more with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>B</td>
<td>None or inconsistent results</td>
</tr>
<tr>
<td>II</td>
<td>C</td>
<td>2 or more with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
<td>None or 1 with consistent results or inconsistent results</td>
</tr>
<tr>
<td>IV–V</td>
<td>D</td>
<td>Not applicable because LOE IV and V studies will never be satisfactory for determination of medical utility</td>
</tr>
</tbody>
</table>

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
# Prognostic Factors I in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE\textsubscript{Ox2001}</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Nodal status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Histological tumor type (colloid, mucinous, tubular etc.)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Grade (Elston &amp; Ellis)</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Age</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Peritumoral lymphatic vessel and vascular invasion (L1 V1)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>pCR after NACT* in (HR+/G3, HER2+, TN)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* NACT = Neoadjuvant Chemotherapy
Reproducibility

- ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)
- Grading: concordance central vs local is 68 % (PlanB, JCO 2016)
- HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20% changes: grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)
- Inter- and intraobserver variability in measurement of ki-67 is high (J Nat. Cancer Institute 2011)
Critical Issues Regarding LoEs for Biomarkers

It needs to be emphasized that the levels of evidence obtained by Oxford-criteria and CTS-criteria cannot be directly compared.

The prospectively-planned retrospective validation of a biomarker (CTS level 1) may be biased by an insufficient number of clinical trial samples used for the biomarker analysis.

This sample collection may not represent the reported outcome of the clinical trial. An optimal percentage of sample needed from clinical trials needed for optimal biomarker validation has not yet been established *

# Prognostic Factors II in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PgR</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>HER2 (IHC, FISH)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>ER / PgR / HER2/ Ki-67 as surrogate markers for molecular subtypes</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>uPA / PAI (Femtelle&lt;sup&gt;®&lt;/sup&gt; ELISA)&lt;sup&gt;§&lt;/sup&gt; in N0</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Proliferation markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 before, during or after treatment</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

§ Validated clinical data only available for this assay
# Commercially Available Molecular Tests

<table>
<thead>
<tr>
<th>Provider</th>
<th>70 gene signature (MammaPrint®) $</th>
<th>21 gene Recurrence score (Oncotype DX®) $</th>
<th>8 gene signature (Endopredict®) $</th>
<th>PAM 50 (Prosigna®) $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agendia</td>
<td>70-gene assay</td>
<td>21-gene recurrence score</td>
<td>11-gene assay</td>
<td>50-gene assay</td>
</tr>
<tr>
<td>Genomic Health</td>
<td></td>
<td></td>
<td>Sividon</td>
<td>NanoString</td>
</tr>
<tr>
<td>Sividon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NanoString</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of tissue</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>fresh frozen (technical validation for FFPE available)</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of tissue</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technique</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microarrays for RNA</td>
<td>qRT-PCR</td>
<td>q-RT-PCR</td>
<td>Direct hybridization</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central lab</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication and population studied</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>prognostic N-/+, &lt; 70 years</td>
<td>prognostic N-/+, ER+ endocrine treated</td>
<td>prognostic (pre-) postmenopausal N-/+, ER+ HER2-endocrine treated</td>
<td>prognostic postmenopausal N-/+, ER+ HER2-endocrine treated</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Validation</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« CE-Mark (fresh tissue and FFPE)</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
<td>CE-Mark</td>
<td>CE-Mark FDA 510(k) Clearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Registration</th>
<th>70-gene assay</th>
<th>21-gene recurrence score</th>
<th>11-gene assay</th>
<th>50-gene assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)« CE-Mark (fresh tissue and FFPE)</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
<td>CE-Mark</td>
<td>CE-Mark FDA 510(k) Clearance</td>
</tr>
</tbody>
</table>

$ Validated clinical data only available for this assay
## Commercially Available Molecular Tests

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

$ Validated clinical data only available for this assay

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

<table>
<thead>
<tr>
<th></th>
<th>TailorX</th>
<th>PlanB</th>
<th>MINDACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period</td>
<td>Median 69 mo</td>
<td>5-yr-DFS</td>
<td>Median 60 mo</td>
</tr>
<tr>
<td>Proportion of low risk patients (study population suitable for chemotherapy)</td>
<td>16 %</td>
<td>15.3 %</td>
<td>23.2 % (high clinical and low genomic risk)</td>
</tr>
<tr>
<td>Test failure rate</td>
<td>n.r.</td>
<td>2.9 %</td>
<td>26 % (fresh frozen tissue)</td>
</tr>
<tr>
<td>Proportion of intermediate risk patients (applies only to OncotypeDX)</td>
<td>67.3 %</td>
<td>60.4 %</td>
<td>n.a.</td>
</tr>
<tr>
<td>10-yr-follow up</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
## Prognostic Factors III in Early Breast Cancer

<table>
<thead>
<tr>
<th>Faktor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tumor cells (DTC, in bone marrow)</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Circulating tumor cells (CTC, in blood, Cell Search®) $</td>
<td>I</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>CTC before NACT (regarding OS, DDFS, LRFI)</td>
<td>I&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

### Multigene assays

- **EndoPredoct®, Prosigna®**
  
  (N0-1, HR+, Her2 -)

- **70 gene signature (MammaPrint®) (N0-1)**

- **Oncotype DX®**
  
  (N0-1, HR+ HER2-, 5 Jahre)

- **IHC4 (central pathology published algorithm) #**

* 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
### Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>
# Neoadjuvant Systemic Chemotherapy Response Prediction II

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene signature</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>(Mammaprint, Endopredict Oncotyp Dx, PAM50 Prosigna$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes*</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>gBRCA in TNBC</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

$ 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 &gt;50% of stroma area)
## Predictive Factors – Endocrine Therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER/PgR status</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>IHC staining intensity (ER/PgR)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 polymorphism</td>
<td>2b</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Ovarian ablation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Aromatase inhibitors vs. Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>ER/PgR/HER2 as single markers</td>
<td>1c</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Lobular subtype</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Ki-67 high (published cutoffs &gt; 11% and &gt;14%)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
### Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE$<em>{Ox2001}$ (§ LoE$</em>{Ox2009}$)</th>
<th>GR (§ CTS)</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER2-Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uPA/PAI1 (Femtelle®) ELISA $</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>21 gene recurrence score (Oncotype DX®) $</td>
<td>I §</td>
<td>B $</td>
<td>+/-</td>
</tr>
</tbody>
</table>

*§ Validated clinical data only available for this assay*
## Prognostic Factors – Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>I</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Prognosis at baseline</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early response assessment (3w)</td>
<td>I</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Therapy decision solely based on dynamics of CTC numbers over time or CTC phenotype</td>
<td>I</td>
<td>A</td>
<td>-*</td>
</tr>
</tbody>
</table>

* Study participation recommended
Prognostic and Predictive Factors (2/21)

Further information:


Guidelines screened:


NCCN 2016: www.nccn.org

General References:

Definition (3/21)

No further information

References:
See general references
Low Absolute Risk Implies Low Absolute Benefit (4/21)

No further information

References:


Quality Criteria (5/21)

No further information

References:

Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination (6/21 and 7/21)

No further information

References:

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

No further information

References:

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

No further information

References:
Also see general references.


Statement: Obesity


Reproducibility (10/21)

No further information

References:


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

No further information

References:

ER/PR


HER2


**Ki-67**


Post-treatment Ki-67:

uPA/PAI-1


Commercially Available Molecular Tests (13/21 and 14/21)

No further information

References:

Endopredict


Breast and Colorectal Cancer Study Group (ABCSG). The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. Br J Cancer. 2013 Dec 10;109(12):2959-64


Mammaprint


Oncotype


Prosigna (ROR / PAM50)


Multiple assays:

**Prospective randomized trials (15/21)**

No further information

**References:**

Mammaprint


Onkotype DX


Several tests

Prognostic Factors III in Early Breast Cancer (16/21)

No further information

References:

DTC


Oncotype


**Endopredict**


Prosigna (ROR, PAM50)


**Mammaprint**


IHC4


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

No further information

References:

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

No further information

References:

TIL


7. Denkert et al, SABCS 2016

PIK3CA

Predictive Factors – Endocrine Therapy (19/21)

No further information

References:


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

No further information

References:

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

Onkotype:


uPA/PAI-1:


Prognostic factors – Metastatic breast cancer (21/21)

No further information

References:


CTC


Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)
Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **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

B-Classification*

B1 = unsatisfactory / normal tissue only
B2 = benign lesion
B3 = lesion of uncertain malignant potential
B4 = suspicion of malignancy
B5 = malignant
   B5a = non-invasive
   B5b = invasive
   B5c = in-situ/invasion not assessable
   B5d = non epithelial, metastatic

* National Coordinating Group for Breast Screening Pathology (NHSBSP), E.C. Working Group on Breast Screening Pathology, S3-Leitlinien
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
### B3-Lesions:

<table>
<thead>
<tr>
<th>Lesion</th>
<th>~PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>20-30%</td>
</tr>
<tr>
<td>Lobular intraepithelial neoplasia (LN/LIN)</td>
<td>0-10%</td>
</tr>
<tr>
<td>Flat epithelial atypia (FEA)</td>
<td>0-10%</td>
</tr>
<tr>
<td>Radial scar / Complex sclerosing lesion</td>
<td>0-10%</td>
</tr>
<tr>
<td>Papilloma without atypia</td>
<td>0-10%</td>
</tr>
<tr>
<td>Cellular fibroepithelial tumors / phyllodes tumors</td>
<td>0%</td>
</tr>
</tbody>
</table>
Management after Minimally Invasive Biopsy

- 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 +
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.**
Strategy after Diagnosis of ADH in Core Biopsy

**ADH in core- / vacuum-assisted biopsy:**
- Open excisional biopsy
- 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

**ADH at margins in resection specimen:**
- No further surgery, if incidental finding accompanying invasive or intraductal carcinoma

---

* Terminal ductal-lobular unit

Oxford / AGO
LoE / GR

3a C ++
5a C +/-
3a C ++
Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)

Stratification of breast cancer risk*

- **Number of Foci:**
  - 1: $RR = 2.33$
  - 2: $RR = 5.26$
  - $\geq 3$: $RR = 7.97$

- **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: $RR = 5.10$
  - $> 55$: $RR = 2.67$

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:**
  Ipsilateral and contralateral enhanced breast cancer risk: 7 x at 10 years
Variants of Lobular Neoplasia

Classical LIN

LIN with comedo type necrosis

Florid LIN

Pleomorphic LIN
LIN with High Risk

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

Strategy after Diagnosis of LIN

- **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
  - Oxford / AGO LoE / GR 2b C ++

- **LIN at margins of resection specimen (BCT):**
  - No further surgery
  - Exceptions:
    - Pleomorphic LIN, florid LIN, or LIN with necrosis
    - Imaging abnormality is not removed
  - Complete resection
  - Oxford / AGO LoE / GR 5 D ++
Flat Epithelial Atypia (FEA)

- **Synonyms:** Columnar cell hyperplasia with atypia, columnar cell metaplasia with atypia, ductal intraepithelial neoplasia grade 1A (DIN 1A)

- **Differential diagnosis:**
  - ADH is discriminated by architectural features (micropapillary, cribriform) → B3
  - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as → B5a

- **Marker lesion:**
  FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, histologic step sectioning and correlation with imaging are mandatory.
Strategy after Diagnosis of FEA

- **FEA in core biopsy/vacuum-assisted biopsy:**
  - Open excisional biopsy
  - Open excisional biopsy may be omitted, with:
    - a small lesion (≤ 2 TDLU* in vacuum biopsy) and complete removal of imaging abnormality

- **FEA at margins in resection specimen:**
  - No further surgery, unless calcifications have not been completely removed

---

* Oxford / AGO LoE / GR
  - 3b C +
  - 5 C +
  - 3b C ++

---

* Terminal ductal-lobular unit
- **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

- Papilloma without atypia in core needle or vacuum biopsies:
  - no further therapy, when biopsy sufficiently representative (100 mm²) and no discordance to imaging

- Multiple papillomas
  - open biopsy

- Papilloma with atypia in core needle or vacuum biopsies:
  - open biopsy

Papilloma at resection margin:
  - no published data available

Oxford / AGO LoE / GR

3a  C  ++
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)*

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

- **Radial scar / CSL in core biopsy/vacuum-assisted biopsy:**
  - Open excisional biopsy
  - Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality

- **Radial scar / CSL at margins in resection specimen:**
  - No further surgery

Oxford / AGO LoE / GR

- Radial scar / CSL in core biopsy/vacuum-assisted biopsy:
  - 3b C +
  - 5a C +

- Radial scar / CSL at margins in resection specimen:
  - 3b C ++
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

FEA, non-atypical papilloma
- Screening mammography

LIN
- Mammography (12 months)

ADH
- Mammography (12 months)

- Women with LIN and ADH should be informed about their elevated risk of breast cancer
Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

- **Tamoxifen for women >35 years** –
  Risk reduction of invasive BrCa and DCIS  
  1a A +

- **Raloxifene 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)
Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen)

NSABP-P1 Study, update 2005

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

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

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

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

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

Visvanathan K et al. JCO 2009;27:3235-3258.
Medical Prevention after Diagnosis of B3 Lesion (Raloxifen)

NSABP-P2 Study, STAR trial 2006

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen : Rate / 1000 WE</th>
<th>Raloxifen Rate / 1000 WE</th>
<th>RR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>All women</td>
<td>4.30</td>
<td>4.41</td>
<td>1.02</td>
<td>0.82-1.28</td>
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<tr>
<td>± LIN</td>
<td>3.76</td>
<td>3.89</td>
<td>1.03</td>
<td>0.81-1.33</td>
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<tr>
<td>+ LIN</td>
<td>9.83</td>
<td>9.61</td>
<td>0.98</td>
<td>0.58-1.63</td>
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<tr>
<td>± ADH</td>
<td>4.06</td>
<td>4.03</td>
<td>0.99</td>
<td>0.76-1.28</td>
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<tr>
<td>+ ADH</td>
<td>5.21</td>
<td>5.81</td>
<td>1.12</td>
<td>0.72-1.74</td>
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</table>

Should only be offered to women with enhanced breast cancer risk:
(Gail ≥1.66%) or postmenopausal

Should not be offered to women:
• With moderate risk > 50 year of age
• With enhanced risk for thrombembolism
# Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors)

## Inclusion criteria:
- **IBIS.2:**
  - Prior ADH, ALH, or LCIS
    - Anastrozole: 154 (8.0%)
    - Placebo: 190 (9.7%)
- **MAP.3:**
  - Prior ADH, ALH, or LCIS:
    - Exemestane: 185 (8.1%)
    - Placebo: 188 (8.3%)

## Results for prior ALH, ADH, LCIS (HR Al vs Plac):
- **IBIS.2:**
  - 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:**
  - Yes: HR=0.61 (0.20–1.82)
  - No: HR=0.26 (0.11–0.64)

---

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

Further information and references:

Pubmed 2010-2016 (plus earlier publications if relevant):


("2005/01/01"[dp] : "2016/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[Title]


**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

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

Lesions of uncertain malignant potential include atypical ductal hyperplasia (ADH), lobular neoplasia (LN), flat epithelial atypia (FEA), atypical papillary proliferations, and lesions with sampling risk because of inhomogeneity, such as phyllodes tumor, cellular fibroadenoma, and radial scars. The lesions with atypical proliferations (ADH, ALH, LCIS, FEA) are regarded both as an indicator of increased risk, but also as precursor lesions, and are part of the low-grade pathway of breast cancers [1-4]. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient, and to decide if the lesion should be excised. The recognition of atypical epithelial proliferation is based on the distinction of hyperplastic from neoplastic lesions, that is on the identification of a clonal process. As a general rule, usual type epithelial hyperplasia is morphologically and phenotypically heterogeneous, while ADH, FEA, and LN are characterized by a homogeneity of cell type and marker expression. With all types of precursor lesions, careful attention must be paid to the pathologic-radiologic correlation for the guidance of the clinical management. B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1.3% discordance for B5 lesions [5].

References:


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

*Further information:*

In this category atypical intraductal hyperplasia (ADH), flat epithelial atypia (FEA), and lobular intraepithelial neoplasia (LN/LIN) are grouped together as lesions of uncertain biological behaviour. Besides these diagnoses papillomas, radial scar and phyllodes-tumour belong to the B3 group. In older studies approximately one-third of CNB results classified as B3 were malignant on excision, but the likelihood of malignancy varied substantially between specific lesion groups. Whereas cases may be selectively managed without surgery, the majority warrant excision biopsy (Rakha 2010, Houssami 2010). No clinical and radiologic findings and/or comprehensive evaluation of multiple histologic parameters on CNB specimen are distinctive enough to predict final classification of equivocal cellular fibroepithelial lesions. In recent years publications demonstrated a decline in PPV except for ADH. This is particularly obvious for LIN, which only rarely shows upgrade to higher lesions in resection when careful correlation between imaging and histology of CNB has been performed. Also papilloma without atypia usually shows no upgrade in resection. With regard to FEA different frequencies of upgrade to higher lesions are published. B3 lesions are diagnosed with less than 10% in mammography screening (6000 core biopsies, with central pathology). But B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1.3% discordance for B5 lesions (Kreipe HH et al 2008).

*Current systematic review:*
Other References:


Management after Minimally Invasive Biopsy (6/25)

Further information:

What kind of treatment has to follow when a B3 diagnosis has been rendered should be individually determined in an interdisciplinary discussion of the imaging findings and the pathology results. Algorithm for quality assurance of minimal invasive guided biopsies.

After a review and quality assessment of 21 studies, diagnostic accuracy of VAB were evaluated. The summary estimates for VAB in diagnosis of breast carcinoma were as follows: sensitivity, 0.981 (95% confidence interval [CI], 0.972-0.987); specificity, 0.999 (95% CI, 0.997-0.999); positive likelihood ratio (PLR), 93.84 (95% CI, 41.55-211.95); negative likelihood ratio, 0.05 (95% CI, 0.03-0.09); diagnostic odds ratio, 1891.7 (95% CI, 683.8-5233.4); underestimate rate of ADH and DCIS were 20.9% (95% CI, 0.177-0.245) and 11.2% (95% CI, 0.098-0.128), respectively. VAB is a highly sensitive and specific biopsy method for evaluating mammographically detected breast in women.

References:


Atypical Ductal Hyperplasia (ADH) (7/25)

Further information:

ADH and breast cancer are associated with postmenopausal hormone treatment. According to the data of the Breast Cancer Surveillance Consortium (USA) rates of ADH decreased from 5.5/10000 mammograms 1999 to 2.4/10000 mammograms in 2005.

Statement: indicator-/ precursor- lesion:
Women have an enhanced breast cancer risk after ADH: one lesion RR 3.88 (95%CI 3.00-4.94), three lesions RR 10.35 (95%CI 6.13-16.4). Less than 45 years at diagnosis of ADH RR 6.78 (95%CI 3.24-12.4).

References:

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 suspicious or malignant characteristics and histological B3 with evidence of epithelial atypia has the highest positive predictive value (50%) (Rhaka et al. 2010). Even in the case of complete removal of microcalcifications there is a risk of 5% of underestimation of malignancy (Penco 2010). An open excisional is recommended with exception of very small lesions (≤ 2 TDLU) and minimal atypia and complete removed imaging abnormality.

ADH in core-/ vacuum-assisted biopsy (LoE 3a)
ADH at margins in resection specimen (LoE 3a)

References:

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

No further information

References:

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 needle, 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 been completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.
References:


Statement: Indicator-/ precursor lesion

**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).

*References:*

LIN with High Risk (12/25)

Further information:

Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, pleomorphic lobular carcinoma in situ (pLCIS) was shown to behave more aggressively compared to classical lobular neoplasia [1]. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. In this respect pLCIS mimics ductal carcinoma in situ (DCIS), but characteristically it is associated with classical LN and not with DCIS. Also, molecular profiling studies have shown that pLCIS is similar to classical LN, supporting its role as a special form of lobular neoplasia. As another approach for risk assessment, a classification of lobular neoplasia into three different grades of severity has been proposed, based on the extent of lobular cancerization [2]. The most severe grade (LIN 3) is called florid lobular carcinoma in situ nowadays [3]. It may be associated with microinvasion [4].

References:

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)


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

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.

References:
Statement: Marker Lesion (LoE 3b)

1. Kunju L: Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? Hum Pathol 2006; 38:35-41
2. Noske A: Flat epithelial atypia is a common subtype of B3 breast lesions and associated with noninvasive cancer but not with invasive cancer in final excision histology. Hum Pathol 2009; Epub ahead of print.
**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)

*References:*

**Papilloma (16/25)**

*Further information:*

Benign intraductal papillomas occur either as a central papilloma originating from the ducts in the subareolar region, or peripherally, and both locations can be either solitary or multiple. Both central and peripheral papillomas are characterized by fibrovascular cores with epithelial and myoepithelial cell layers. Central intraductal papillomas with a predominant or exclusive glandular differentiation are called ductal adenoma [1]. Intraductal papillomas and ductal adenomas may show regressive changes, such as sclerosis or infarction, also also epithelial or myoepithelial hyperplasia or squamous or apocrine metaplasia. These changes may cause diagnostic difficulties in core needle biopsy [2]. The term papillomatosis is not used in the WHO classification of the breast, because was historically used both for usual type ductal hyperplasia and for papillomas.

Atypical epithelial proliferations (ADH and DCIS) may occur in papillomas, and are usually of low grade. As with atypical intraductal proliferative lesions, the distinction of ADH and DCIS within a papilloma rests with quantitative criteria [1]. An intraductal papilloma with ADH is diagnosed when the atypical epithelial proliferation is < 3 mm, while larger atypical epithelial proliferations within a papilloma fulfill the criteria of an intraductal papilloma with low grade [3]. This definition replaces alternative terminologies that were focused on the proportion of atypical cells (30% or 90%) within a papilloma. An intermediate or high grade DCIS within a papilloma can be diagnosed regardless of the extent of atypia.

*References:*

Further information:

A policy of open excisional biopsy after the diagnosis of a central papilloma has been recommended by the European guidelines for quality assurance in breast cancer screening. However, this recommendation has been questioned by newer studies. The risk of up-grade is to be considered very low in central papilloma without atypia and not sufficient to justify routine surgical resection.

References:


Radially Sclerosing Lesion (18/25)

No further information

References:


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

No further information

References


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

Further information:

Women with ADH and LIN need to be informed about their elevated risk for breast cancer. Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolute terms, helping women to make an informed decision to her personal needs and values. Atypia patients who drank alcohol and had a first-degree relative with breast cancer have an increased risk of breast cancer compared to those without atypia [1].

References:

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.

References:


Studies on medical prevention for women at increased risk that included women with LIN and ADH are in **bold**.
Tamoxifen für Frauen > 35 Jahre –Reduktion von DCIS und invasivem Karzinom (LoE 1a A AGO +)

NSABP.P1:


IBIS.1


Royal Marsden
Italian Trial

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

MAP.3


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

No further information

References:

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:

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

No further information

References:

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

No further information

References:

Exemestane for breast-cancer prevention in postmenopausal women.


Chemoprevention for breast cancer.

1. Bozovic-Spasojevic I¹, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F²
Ductal Carcinoma in Situ (DCIS)
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
## Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

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

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

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

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

A. Fancellu¹, R. M. Turner², J. M. Dixon⁴, A. Pinna¹, P. Cottu¹ and N. Houssami³

¹Department of Clinical and Experimental Medicine, Unit of General Surgery 2, Clinica Chirurgica, University of Sassari, Sassari, Italy; ²School of Public Health and Community Medicine, The University of New South Wales; and ³Screening and Test Evaluation Programme, School of Public Health, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia and ⁴Breakthrough 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: afancell@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
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.
The True Impact of Breast MRI on the Management of In-Situ Disease: More is Not Better

Michael Lallemand MD*1, Morgan Barron MD2, Jason Bingham MD3, Andrew Mosier MD4, Mark Hardin MD5, Vance Sohn MD6

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

Michael Lallemand MD*,1, Morgan Barron MD2, Jason Bingham MD3, Andrew Mosier MD*4, Mark Hardin MD5, Vance Sohn MD6

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.
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
## 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

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

$^3$ adjusted for year of diagnosis, age of diagnosis, ethnicity, income, ER-status, tumor size and grade
# Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years

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

## Breast Conserving Surgery Alone

<table>
<thead>
<tr>
<th>Time period</th>
<th>5 year</th>
<th>10 year</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1998</td>
<td>19.1% (15.6 - 23.2%)</td>
<td>26% (22.0 - 30.7%)</td>
<td>1.0</td>
<td>----</td>
</tr>
<tr>
<td>1999-2010</td>
<td>8.9% (7.1 - 11.3%)</td>
<td>19% (14.9 – 23.1%)</td>
<td>0.59</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

## Breast Conserving Surgery and Radiotherapy

<table>
<thead>
<tr>
<th>Time period</th>
<th>5 year</th>
<th>10 year</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-1998</td>
<td>6.4% (4.1 - 9.8 %)</td>
<td>13% (9.3 - 17.1 %)</td>
<td>1.0</td>
<td>----</td>
</tr>
<tr>
<td>1999-2010</td>
<td>4.9% (3.7 – 6.5 %)</td>
<td>11% (8.7- 14.2 %)</td>
<td>0.84</td>
<td>0.04</td>
</tr>
</tbody>
</table>
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.
Surgical Treatment for Histologically Proven DCIS I

- Excisional biopsy (wire guided)  
  Oxford / AGO LoE / GR: 2b B ++

- Bracketing wire localization in large lesions  
  Oxford / AGO LoE / GR: 5 D +

- Specimen radiography  
  Oxford / AGO LoE / GR: 2b B ++

- Intraoperative ultrasound (visible lesion)  
  Oxford / AGO LoE / GR: 3a C +/-

- Immediate re-excision for close margins (specimen radiography)  
  Oxford / AGO LoE / GR: 1c B ++

- Intraoperative frozen section  
  Oxford / AGO LoE / GR: 5 D - -

- Interdisciplinary board presentation  
  Oxford / AGO LoE / GR: 2b C ++

Open biopsy in suspicious lesions (mammographical microcalcifications, suspicious US, MRI etc.) without preoperative needle biopsy should be avoided.
# Surgical Treatment for Histologically Proven DCIS II

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologically clear margins (R0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocal DCIS: BCS if feasible</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Re-excision required for close margin ≤ 2 mm in paraffin section)</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Mastectomy*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large lesions confirmed by multiple biopsies; no clear margins after re-excision</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>SNE*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>3b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In case of DCIS in the male breast</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>ALND</td>
<td>2b</td>
<td>B</td>
<td>- -</td>
</tr>
</tbody>
</table>

* Patients who present with a palpable mass have a significantly higher potential for occult invasion (26%), multicentricity and local recurrence.
DCIS – Prognostic Factors for the Incidence of Ipsilateral Recurrence

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

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

## Radiotherapy after:
- Breast conserving surgery (BCS)
- Mastectomy

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

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

* Side effects and disadvantages of radiotherapy must be balanced against risk reduction. Omitting radiotherapy implies elevated risk for local recurrence without effect for overall survival even in the subset of „good risk” patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected

** Analysis in ongoing trials
Cochrane Analysis
Radiation after Surgery (all/with Radiation after Breast Conserving Surgery)

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

## DCIS Postoperative Systemic Treatment

- **Tamoxifen (only ER+)**
  - Oxford / AGO LoE / GR 1a A +/-

- **Aromatase inhibitor (only ER+) in postmenopausal women only**
  - Oxford / AGO LoE / GR 1b A +/-

- **Trastuzumab (only Her2+)**
  - Oxford / AGO LoE / GR 5 D --

*Indication for treatment depends on risk factors, side effects and patient preference*
Local Recurrence of DCIS after Tumorectomy w/o Irradiation

After radiation

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

No radiation after first tumorectomy

- Treatment like primary disease

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


Stereotaktische Stanzbiopsie / Vakuumbiopsie (VAB)


Präparateradiographie
Setzen eines Markierungscips in der Biopsieregion, wenn die Läsion komplett entfernt wurde

MRT zur Festlegung der Ausdehnung

Klinische Untersuchung
Feinnadelpunktion / dukale Lavage
Interdisziplinäre Tumorboard-Präsentation
MRT and DCIS (4/24)

No further information

No references
MRI and DCIS (5/24-10/24)

No further information

No references
Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ (11/24-12/24)

No further information

References:

1. Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD; JAMA Oncol. doi:10.1001/jamaoncol.2015.2510 Published online August 20, 2015.
Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years (13/24)

No further information

Reference:

1. Preeti Subhedar, MD1, Cristina Olcese, BS1, Sujata Patil, PhD2, Monica Morrow, MD, FACS1, and Kimberly J. Van Zee, MS, MD, FACS1; Ann Surg Oncol (2015) 22:3273–3281
General Therapeutic Principles (14/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

References:

5. Laura Esserman, Christina Yau. Rethinking the Standard for Ductal Carcinoma In Situ Treatment. JAMA Oncology Published online August 20, 2015.
Surgical Treatment for Histologically Proven DCIS I (15/34)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

Exzision (drahtmarkiert)


Flankierende Drahtmarkierung bei großen Läsionen

Präparatradiographie
Intraoperative Sonographie (darstellbarer Befund)

Sofortige Nachresektion bei knappen Resektionsrändern (Präparateradiographie)


Intraoperative Schnellschnittdiagnostik
Interdisziplinäre Tumorboard-Präsentation
Surgical Treatment for Histologically Proven DCIS II (16/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

Histologisch freie Resektionsränder (pR0)

Multifokalität: BET falls möglich (inkl. RT)


Nachresektion bei knappem Resektionsrand (< 2 mm im Paraffinschnitt)


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


SNE*
Mastektomie
DCIS beim Mann


BET


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

No further information

References:

Resektionsränder
Residualer tumorassoziierter Mikrokalk
Alter
Größe
Grading
Komedonekrose
Architektur


Diagnostische Methode

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

Fokalität


(mod.) Van Nuys Prognose Index und MSKCC Nomogramm

7. Silverstein MJ, Lagios MD. Choosing Treatment for Patients With Ductal Carcinoma In Situ: Fine Tuning the University of Southern California/Van Nuys Prognostic Index. J natl Cancer Inst Monogr 2010; 41: 193-196

Palpables DCIS
Palpabel + COX-2+p16+Ki-67+
Palpabel + ER-, HER2, +Ki-67+
HER2-Überexpression
ER/PgR (positiv vs. negativ)
DCIS-Score

2. Sarah Patricia Cate, Alyssa Gillego, Manjeet Chadha, John Rescigno, Paul R. Gliedman, Ilana Kats, Susan K. Booolbol. Does the Oncotype DCIS score impact treatment decisions? J Clin Oncol 31, 2013 (suppl 26; abstr 91)


DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom


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

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)


10. Schwartz GF, Solin LJ, Olivotto IA, Ernster VL, Pressman PI.
12. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial.


34. Australian New Zealand Clinical Trials Registry website. The Trans Tasman Radiation Oncology Group (TROG) 07.01: A randomised phase III study of radiodoses and fractionation schedules in non-low risk Ductal Carcinoma In


Mastektomie


Sonderformen der Radiotherapie:
Teilbrustbestrahlung


10. John Paul Einck, Steven E. Finkelstein, Ben Han, Robert Hong, Lydia T. Komarnicky, Robert R. Kuske, Sudha B. Mahalingam, Constantine Mantz, Serban Morcovescu, Stephen S. Nigh, Kerri L. Perry, Jondavid Pollock, Jay E. Reiff, Daniel Scanderbeg, Jon F. Strasser, Catheryn M. Yashar, SAVI Collaborative Research Group; Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA; 21st Century Oncology of Arizona, Translational Research Center, Scottsdale, AZ; South Florida Radiation Oncology, LLC, Boynton Beach, FL; Virginia Hospital Center, Arlington, VA; Drexel University College of Medicine, Philadelphia, PA; Arizona Breast Cancer Specialists, Scottsdale, AZ; The Christ Hospital Cancer Center, Cincinnati, OH; 21st Century Oncology, Translational Research Consortium (TRC), Fort Myers, FL; Texas Oncology, Denton, TX; Northwest Community Hospital Cancer Services, Arlington Heights, IL; Kerri Perry, MD, Denton, TX; Schiffler Cancer Center, Wheeling, WV; Helen F. Graham Cancer Center - Christiana Care Health System, Newark, DE. Accelerated partial-breast irradiation using strut-based brachytherapy in ductal carcinoma in situ patients: A report on 321 patients with median 25-month follow-up. J Clin Oncol 31, 2013 (suppl 26; abstr 92)


Bei Patientinnen unter 45-50 Jahren
Cochrane Analysis – Radiation after Surgery (20/24)

*No further information*

*No references*
No further information

References:

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

No further information

Reference:

DCIS Postoperative Systemic Treatment (23/24)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

Tamoxifen (nur ER+, nur BET)


AI (wenn postmenopausal und Kontraindikationen gegen Tamoxifen)

Andere endokrine Optionen Trastuzumab (nur HER2+)


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


Sekundäre Tumorektomie führt zu Rezidiven in bis zu 30 % der Fälle (NSABP B17)


Keine Radiotherapie  
Therapieindikation wie bei primär Erkrankung
Breast Cancer Surgery
Oncological Aspects
Breast Cancer Surgery
Oncological Aspects

- **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
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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpation</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Ultrasound (breast &amp; axilla)</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Minimal invasive biopsy*</td>
<td>1c A +</td>
</tr>
<tr>
<td>MRI**</td>
<td>1c B +/-</td>
</tr>
</tbody>
</table>

* 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

- **History and physical examination**
  - Only recommended in high metastatic potential and / or with symptoms:
    - **Chest X-ray**
    - **Liver ultrasound**
    - **CT-scan**
    - **Bone-scan**
    - **FDG-PET or FDG-PET / CT**
    - **Whole body MRI**

<table>
<thead>
<tr>
<th>Test</th>
<th>LoE</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>Liver ultrasound</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>CT-scan</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>Bone-scan</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>FDG-PET or FDG-PET / CT</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Whole body MRI</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>
Evidence of Surgical Procedure

- Survival rates after lumpectomy + XRT are equivalent to those after (modified) radical mastectomy
- Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy
- Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy
- 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

Oxford / AGO LoE / GR

1a A
1b A
2b B
2b C
Breast Conservation: Surgical Technical Aspects

- **Non-palpable lesion**
  - Wire guided localisation
  - Radionuclide guided localisation
  - Specimen radiography or ultrasound

- **Tumor-free margins required**
  (also in unfavorable biology „no cells on ink“ are enough)

- **Immediate intraoperative re-excision for close margins**
  (specimen radiography and/or intra-operative pathology)

- **Re-excision required for involved margins**
  (paraffin section)

- **Therapeutic stereotactic excision alone**

- **Ultrasound guided surgery to prevent re-excision**

- **Intraop. margin evaluation with margin probe**

Oxford / AGO LoE / GR

- Non-palpable lesion:
  - Wire guided localisation: 2b B ++
  - Radionuclide guided localisation: 2b B +/-
  - Specimen radiography or ultrasound: 2b B ++

- Tumor-free margins required:
  - 2a A ++

- Immediate intraoperative re-excision for close margins:
  - 1c B ++

- Re-excision required for involved margins:
  - 3b C +

- Therapeutic stereotactic excision alone:
  - 4 D - -

- Ultrasound guided surgery to prevent re-excision:
  - 1a A +/-

- Intraop. margin evaluation with margin probe:
  - 1b A +/-
Breast Conservation Surgery (BCS)

- 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“
### Axillary Lymph Node Dissection I

**Axillary lymph node dissection (≥10 LN)**
- To improve survival
- For staging
- For local control

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

**Axillary lymph node dissection indicated, but not feasible**
- Radiation according to AMAROS-trial

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* Study participation recommended
## Axillary Intervention Before or After NACT

### SLNB before or after NACT in cN0

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### Further surgical procedures depending on SLNB status

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<td></td>
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<td></td>
<td>2b</td>
<td>B</td>
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</tbody>
</table>
Improvement of the False-Negative Rate of SLNB after NACT in Patients with (cN+) (FNA/CNB)

- Removal of > 2 SLNs
- Combined tracer
- IHC and serial sections
- LN localisation

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

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

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>1b A</td>
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<tr>
<td>2a B</td>
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<tr>
<td>2b A</td>
<td>++</td>
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<td>2b B</td>
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<td>3b B</td>
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<td>5 D</td>
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<td>3b B</td>
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<td>2b B</td>
<td>+</td>
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<tr>
<td>3b B</td>
<td>+</td>
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<tr>
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<td>Oxford / AGO LoE / GR</td>
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<td>---------------------------------------------------------------------------</td>
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<tr>
<td>During pregnancy and / or breast feeding (no blue dye)</td>
<td>3 C +</td>
</tr>
<tr>
<td>After previous tumor excision</td>
<td>2b B +</td>
</tr>
<tr>
<td>Previous major breast surgery (e.g. reduction mammoplasty, mastectomy)</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Ipsilateral breast recurrence after prior BCS and prior SNE</td>
<td>4 D +/-*</td>
</tr>
<tr>
<td>SN in the mammarian internal chain</td>
<td>2b B -</td>
</tr>
<tr>
<td>After axillary surgery</td>
<td>3b B +/-*</td>
</tr>
<tr>
<td>Prophylactic bilateral / contralateral mastectomy</td>
<td>3b B - -</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>3b C -</td>
</tr>
</tbody>
</table>

* Lymph node scintigraphy is necessary
Sentinel Lymph Node Excision (SNE): Marking

- $^{99m}$Tc Kolloid
- Blue dye
- Methylen blue
- Indocyanin green (ICG)*
- SPIO#

**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 +/-

# SPIO: Superparamagnetic Iron Oxide

* Study participation recommended
Procedure after Neoadjuvant Therapy

- Marking of tumor in a timely manner
- Surgery
- Microscopically clear margins
- Tumor resection in the new margins

For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“
## Adjuvant Therapy after Primary Surgery

- **Start adjuvant systemic therapy and RT** as soon as possible (a.s.a.p.) after surgery  
  - Oxford / AGO LoE / GR: 1b A ++

- **Start of adjuvant chemotherapy after surgery a.s.a.p., and prior to RT**  
  - Oxford / AGO LoE / GR: 1b A ++

### Without cytotoxic therapy:

- **Start irradiation 6-8 weeks after surgery**  
  - Oxford / AGO LoE / GR: 2b B ++

- **Start endocrine therapy after surgery and a.s.a.p.**  
  - Oxford / AGO LoE / GR: 5 D ++

- **Tamoxifen concurrent with radiotherapy**  
  - Oxford / AGO LoE / GR: 3b C +

- **AI concurrent with radiotherapy**  
  - Oxford / AGO LoE / GR: 3b C +
Breast Cancer Surgery Oncologic Aspects (2/16)

Further information and references:

Update Januar 2017

Screened consensus conference:
Cochrane library:
Breast Cancer Surgery Oncologic Aspects (3/16)

No further information

No references
Pretherapeutic assessment (4/16)

No further information

References:

Statement: Palpation

1. GCP

Statement: General


Statement: Mammography / Ultrasound


Statement minimal invasive biopsy

Statement MRI

6. Houssami N, Hayes DF Review of preoperative magnetic resonance imaging (MRI) in breast cancer: Should MRI be performed on all women with newly diagnosed early stage breast cancer. CA Cancer J Clin 2009; 59:290-302


Pre-operative staging (5/16)

No further information

References:

Statement: history and physical examination

1. GCP

Statement: high metastatic potential / symptoms

Evidence of surgical procedure (6/16)

No further information

References:

Statement: lumpectomy – mastectomy


Statement: skin sparing mastectomy


Statement: Nipple sparing mastectomy


**Breast Conservation, Surgical Technical Aspects (7/16)**

_No further information_

**References:**

Statement: Wire guided ...


Statement: Radioguided ...

Statement: specimen radiography


Statement: tumor free margins ...


Statement: tumor free margins in intrinsic subtypes


Statement: ... re-excision ...

Statement: stereotactic excision alone ...


Statement: Intraoperative ultrasound...


Statement: Margine probe

1. Freya Schnabel, Susan K. Boolbol, Mark Gittleman, Tami Karni, Lorraine Tafr, Sheldon Feldman, Alice Police, Neil B. Friedman, Scott Karlan, Dennis Holmes, Shawna C. Willey, Moshe Carmon, Kristen Fernandez, Stephanie Akbari, Jay Harness, Lisa Guerra, Thomas Frazier, Karen Lane, Rache M. Simmons, Alison Estabrook, and Tanir Allweis. A Randomized Prospective Study of Lumpectomy Margin Assessment with Use of MarginProbe in
Breast Conservation Surgery (8/16)

No further information

References:

Statement: Multicentricity


Statement: positive microscopic ...


Statement: Inflammatory Carcinoma


Statement: general

Axillary Lymph Node Dissection I (9/16)

No further information

References:

Statement: Axillary lymph node dissection


Statement AMAROS-trial

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

No further information

References:

Statement: Axillary lymph node dissection

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


Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy


**Axillary Intervention Before or After NACT (11/16)**

No further information

**References:**

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

No further information

References:

Statement: SLNB


Statement: DCIS


Statement: elderly


Statement: preoperative FNA / core biopsy of suspicious lymph nodes


Statement: Lymphedema

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

No further information

References:

Statement: pregnancy


Statement: mammarian internal

Statement: prophylactic mastectomy


Statement: After previous tumor excision


Statement: previous major breast surgery

1. Intra et al. Sentinel lymph node biopsy is feasible even after total mastectomy. J Surg Oncol 2007 Feb 1;95(2):175-9

Statement: Ipsilateral breast recurrence after prior BCS and prior SLNB


Statement: inflammatory breast cancer


Statement: Others


Sentinel Lymph node excision: Marking (14/16)

No further information

References:

Statement radiotracer/blue dye:


Statement: methylene blue


Statement: ICG:


Statement: SPIO:


Statement: General


Statement: Comparisons

Procedure after Neoadjuvant Therapy (15/16)

No further information

References

Statement: clip marking


Statement: operation and tumor resection in new margins


Statement: tumor free margins ...

Ajuvant Therapy after Primary Surgery (16/16)

No further information

References:

Statement: Timing of radiation and chemotherapy


Statement: Tamoxifen concurrent with chemotherapy


Statement AI concurrent with radiotherapy

Oncoplastic and Reconstructive Surgery
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

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

- Tumor adapted reduction mammaplasty  
  Oxford / AGO LoE / GR  
  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
Algorithm of Breast Reconstruction

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 prosthesis reconstruction
N.B.: Increased complication rate
Breast Reconstruction
General Considerations

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

AGO: ++
### Postmastectomy Reconstruction

- **Use of silicone filled breast implants**
  - Oxford / AGO LoE / GR: 2a B +

- **Autologous tissue reconstruction**
  - Oxford / AGO LoE / GR: 2a B +

- **Pedicled tissue reconstruction**
  - Oxford / AGO LoE / GR: 2a B +

- **Free tissue reconstruction**
  - Oxford / AGO LoE / GR: 2a B +

- **Autologous tissue combined with implants**
  - Oxford / AGO LoE / GR: 3a C +

**Attention:** BMI >30, smoking status, diabetes, RT, age, bilateral mastectomy
Timing of Reconstruction

- **Immediate BR**
  - Mandatory: SSM / NSM
  - Avoidance of a postmastectomy syndrome

- **Delayed BR**
  - No interference with adjuvant procedures (CHT, RT)
  - Disadvantage: loss of skin envelope

- „Delayed-immediate“ BR

---

**Oxford / AGO LoE / GR**

- Immediate BR: 3b, B, ++
- Delayed BR: 3b, B, ++
- „Delayed-immediate“ BR: 3b, B, +/-
Timing of Implant Based Reconstruction and Radiotherapy

- Implant reconstruction (IR)
  - IR without radiotherapy (RT)  
    - Level of Evidence / Grade of Recommendation: 2a B ++
  - IR prior to RT / following PBRT (higher complication rate)  
    - Level of Evidence / Grade of Recommendation: 2a B +
  - IR following MX and RT  
    - Level of Evidence / Grade of Recommendation: 2b B +/-
  - IR following Mx for local relapse after BCT  
    - Level of Evidence / Grade of Recommendation: 2a B +/-
  - Periop. antibiotic therapy (at least 24 h)  
    - Level of Evidence / Grade of Recommendation: 2b B +

*MX = Mastektomie
Tissue Replacement Techniques and Meshes

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

* LDF = Latissimus dorsi flap

# Participation in register study recommended
Lipotransfer

- Lipotransfer after MX and breast reconstruction
  - Oxford / AGO LoE / GR: 2a B +

- Lipotransfer after breast-conserving therapy
  - Oxford / AGO LoE / GR: 2a B +

- Autologous adipose derived stem cells (ASCs)-enriched fat grafts
  - Oxford / AGO LoE / GR: 5 D -
## Postmastectomy Pedicled Reconstruction

**Reconstruction (BR) with autologous tissue**

- **TRAM, latissimus-dorsi-flap** (both can be performed as a muscle-sparing technique)
  - Level of Evidence: 3b, Grade of Recommendation: C, +

- **Delayed TRAM in risk patients**
  - Level of Evidence: 3a, Grade of Recommendation: B, +

- **Ipsilateral pedicled TRAM**
  - Level of Evidence: 3b, Grade of Recommendation: A, +

**Radiotherapy:**

- **BR following RT**
  - Level of Evidence: 2a, Grade of Recommendation: B, +

- **BR prior to RT**
  - Level of Evidence: 2a, Grade of Recommendation: B, +/-
  (more fibrosis, more wound healing problems, more liponecrosis)
Free Tissue Transfer

Free tissue transfer

- DIEP-flap
- Free TRAM-flap
- SIEA-flap
- Gluteal Flaps (SGAP-/IGAP-flap/FCI)
- Free gracilis flap (TMG)

**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
Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used.

Autologous abdominal-based reconstructions have the highest satisfaction in all patient groups without any difference.

Donor site morbidity (e.g. impaired muscle function) has to be taken into consideration in all flap techniques.
Flap-Implant Combination

LDF* + implant
- IR following RT
- IR prior to RT
Other flaps + implant

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

Disadvantage:
- Muscle contraction (LDF)

* LDF = Latissimus dorsi flap
Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction

- **Skin sparing mastectomy (SSM/NSM)**
  - Safe (same recurrence rate as MX)
  - Higher QoL for patients
  - NAC can be preserved under special conditions
    - Feasible after mastopexy / reduction mammoplasty

- **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
Risk Reducing Bilateral Mastectomy in Healthy Women (RRBM)

- RRBM reduces breast cancer incidence
- RRBM in deleterious BRCA1/2 mutation
- 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)
- High risk and no BRCA counselling in specialized centre*
- Non-directive counselling prior to RRBM
- RRBM should be considered with other prophylactic surgical options incl. bilateral salpingoophorectomy (BSO)
- Further need for education of physicians regarding possibilities and advantages of RRBM

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th></th>
<th>RRBM reduces breast cancer incidence</th>
<th>1b</th>
<th>A</th>
<th>++</th>
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<tr>
<td></td>
<td>RRBM in deleterious BRCA1/2 mutation</td>
<td>2a</td>
<td>B</td>
<td>+*</td>
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<tr>
<td></td>
<td>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)</td>
<td>4</td>
<td>D</td>
<td>+/-*</td>
</tr>
<tr>
<td></td>
<td>High risk and no BRCA counselling in specialized centre*</td>
<td>5</td>
<td>D</td>
<td>- -</td>
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<tr>
<td></td>
<td>Non-directive counselling prior to RRBM</td>
<td>2b</td>
<td>B</td>
<td>++*</td>
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<td>RRBM should be considered with other prophylactic surgical options incl. bilateral salpingoophorectomy (BSO)</td>
<td>2a</td>
<td>A</td>
<td>++*</td>
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<tr>
<td></td>
<td>Further need for education of physicians regarding possibilities and advantages of RRBM</td>
<td>1b</td>
<td>A</td>
<td>++</td>
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</tbody>
</table>
Types of Risk Reducing (bilateral) Mastectomy (RRBM)

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

- Simple mastectomy
- RRBM by SSM*
- RRBM by NSM* (NAC# sparing)
- Contralateral prophylactic MX

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


Verwendete Guidelines zu Diagnostik und Therapie des Mammakarzinoms:

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 Empfehlungsdiaps 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

References:

Algorithm of Breast Reconstruction (5/21)

No further information

References:

Breast Reconstruction - General Considerations (6/18)

No further information

References:

1. AWMF Leitlinien: S3-LL. Brustrekonstruktion mit Eigengewebe. Registernummer 015 – 075, Stand: 01.04.2015 , gültig bis 31.03.2020
**Postmastectomy Reconstruction (7/18)**

No further information

**References:**

**Timing of Reconstruction (8/18)**

No further information

**References:**


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

No further information

References:


**Tissue replacement techniques and Meshes (10/18)**

*No further information*

**References:**


4. Clinical outcome and patient satisfaction with the use of bovine-derived acellular dermal matrix (SurgiMend™) in implant based immediate reconstruction following skin sparing mastectomy: A prospective observational study in a single centre. Headon H¹, Kasem A¹, Manson A¹, Choy C¹, Carmichael AR¹, Mokbel K². Surg Oncol. 2016 Jun;25(2):104-10.


**Lipotransfer (11/18)**

Further information:

**Reference:**

1. AWMF-Leitlinie „Autologe Fettttransplantation“, Klasse: S2k Registernummer: 009/017, 11/2015
Postmastectomy (pedicled) Reconstruction (12/18)

No further information

References:


Free Tissue Transfer (13/18)

No further information

References:

6. Tamoxifen may increase the risk of microvascular flap complications. Surgeons should consider temporarily stopping the drug 28 days before microsurgical breast reconstruction. Kelley BP Valero V Yi M Kronowitz SJ Plast Reconstr Surg. 2012 Feb;129(2):305-14
Pedicled vs. Free Tissue Transfer (14/18)

No further information

Reference:

1. AWMF Leitlinien: S3-LL. Brustrekonstruktion mit Eigengewebe. Registernummer 015 – 075, Stand: 01.04.2015 , gültig bis 31.03.2020
Flap-Implant Combination (15/18)

No further information

References:


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

No further information

References:


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

No further information

References:

Types of Risk Reducing Mastectomy (18/18)

No further information

References:


Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **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
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
Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Assessment of menopausal status

- Menstruation history +
- FSH, E2 ++
Adjuvant Endocrine Therapy

Standard therapy for endocrine responsive / doubtfully responsive tumors:

- Endocrine therapy
  - Oxford / AGO LoE / GR
  - 1a A ++

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

- Endocrine responsive & doubtfully Endocrine therapy
  - Oxford / AGO LoE / GR: 1a A ++

- Endocrine therapy Sequentially after CT
  - Oxford / AGO LoE / GR: 2b C ++

- Non-responsive: No endocrine therapy
  - Oxford / AGO LoE / GR: 1a A ++
General Principles in Adjuvant Endocrine Therapy
AGO ++

- Adjuvant endocrine therapy is divided 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 Al) 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.
### Premenopausal Patients

**Adjuvant Endocrine Therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>AGO LoE / GR</th>
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<tbody>
<tr>
<td><em><em>Tamoxifen</em> 5 -10 years</em>*</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td><strong>GnRH alone</strong></td>
<td>1a</td>
<td>B +</td>
</tr>
<tr>
<td>(only, if relevant contraindication for Tam)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In patients with ovarian function (within 8 mon.) after adjuvant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td># OFS (ovarian function suppression)</td>
<td>1b</td>
<td>B +/-</td>
</tr>
<tr>
<td>5 years + Tam 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in patients &lt; 35 y.</td>
<td>1b</td>
<td>B +</td>
</tr>
<tr>
<td># OFS 5 years + AI 5 years</td>
<td>1b</td>
<td>B +/-</td>
</tr>
</tbody>
</table>

* Treat as long as tolerable and premenopausal

# Increased side effects may impair compliance. Higher compliance to TAM alone is more effective, than addition of GNRH or treatment with GNRH+AI and impaired compliance.
Postmenopausal Patients
Initial Adjuvant Endocrine Therapy
(Years 0-5)

- **AI for first 5 years**
  - 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
  - AI (2-3 yrs.) followed by Tam to complete 5 years
- **Tamoxifen 20 mg/d for 5 yrs.**

---

### Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>LoE</th>
</tr>
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<tr>
<td>AI for first 5 years</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Especially in case of lobular cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk of recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential therapy for first 5 years</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Tam (2-3 yrs.) followed by AI to complete 5 years</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>AI (2-3 yrs.) followed by Tam to complete 5 years</td>
<td>1b</td>
<td>C</td>
</tr>
<tr>
<td>Tamoxifen 20 mg/d for 5 yrs.</td>
<td>1a</td>
<td>A</td>
</tr>
</tbody>
</table>
Postmenopausal Patients
Extended Adjuvant Endocrine Therapy
(Years 6-10)

- 2.5 - 5 years AI after 5 years Tamoxifen in patients with validated postmenopausal status in the course of therapy
- 5 years Tamoxifen after 5 years Tamoxifen (in case of higher risk)
- After 2 - 5 years Tamoxifen AI for 2.5 - 5 years
- After initial therapy with AI further prolongation of endocrine therapy with AI*
  - high risk and good tolerability of the AI
  - low risk, poor tolerability of the AI

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Risk Level</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 - 5 years AI after 5 years Tamoxifen</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>5 years Tamoxifen after 5 years Tamoxifen</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>After 2 - 5 years Tamoxifen AI for 2.5 - 5 years</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>After initial therapy with AI further prolongation of endocrine therapy with AI*</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* Up to date, no impact on OS
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

- For ovarian function protection
  CT + GnRHa
  (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)

- Fertility preservation counselling

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

Oxford / AGO LoE / GR

1a B +

4 C ++

4 C +
TEXT / SOFT Joint Analysis

**TEXT**

- Premenopausal Patients with HR+ BC ≤ 12 wks after surgery (N = 2672)

**SOFT**

- Premenopausal patients with HR+ BC ≤ 12 wks after surgery (if no chemo) or ≤ 8 mos after chemo (N = 3066)

**Joint Analysis**

- Tamoxifen 20 mg/day + OFS* (n = 1328)

- Tamoxifen 20 mg/day + OFS* (n = 1016)

- Exemestane 25 mg/day + OFS* (n = 1014)

- Tamoxifen 20 mg/day

- Exemestane 25 mg/day

- Exemestane 25 mg/day + OFS* (n = 1332)

- Exemestane + OFS* (n = 2346)

- Tamoxifen + OFS* (n = 2344)

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

Median follow-up: 5.7 yrs

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

<table>
<thead>
<tr>
<th></th>
<th>10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years 5-9</strong></td>
<td>1.08 (0.85-1.38) p = 0.07</td>
<td>0.92 (0.77-1.09) p = 0.0002</td>
<td>0.97 (0.84-1.15)</td>
</tr>
<tr>
<td><strong>Years 10+</strong></td>
<td>0.75 (0.63-0.90) p = 0.07</td>
<td>0.75 (0.63-0.90) p = 0.0002</td>
<td>0.75 (0.65-0.86) p = 0.00004</td>
</tr>
<tr>
<td><strong>All years</strong></td>
<td>0.88 (0.74-1.03) p = 0.1</td>
<td>0.83 (0.73-0.86) p = 0.004</td>
<td>0.85 (0.77-0.94) P= 0.001</td>
</tr>
</tbody>
</table>

nach Grey et al ASCO 2013 
J Clin Oncol 31, 2013 (suppl. Abstr 5)
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.
Epub 2016 Feb 18.
Aromatase Inhibitors in Adjuvant Therapy
Overview over Published Trials: Initial Therapy (years 1-5)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>AI</th>
<th>Indication</th>
<th>Pts</th>
<th>F/U mo</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>ATAC Trialists’ Group 2010</td>
<td>A</td>
<td>upfront vs T</td>
<td>6241</td>
<td>120</td>
<td>HR + patients: DFS HR 0.86, p=0.003 TTR -0.79, p=0.0002 TTDR 0.85, p=0.02</td>
<td>HR 0.87 p=0-4</td>
<td>SAE T&gt;A</td>
<td>only anastrozole vs tamoxifen, combination arm stopped after first analysis: ER+PR=ER+PR+ (Cuzick 2010) QoL→ (Cella 2006)</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>BIG 1-98 Collaborative Group 2011</td>
<td>L</td>
<td>upfront² vs T</td>
<td>4922</td>
<td>97</td>
<td>DFS = 0.86 P = 0.007</td>
<td>P = 0.048</td>
<td>SAE T=L</td>
<td>L&gt;T in particular in case of N+</td>
</tr>
<tr>
<td>NCIC CTG MA.27</td>
<td>Goss 2010</td>
<td>E</td>
<td>upfront vs A</td>
<td>7576</td>
<td>49</td>
<td>EFS HR 1.02 DDFS HR 0.95</td>
<td>ns</td>
<td>Osteoporosis A&gt;E</td>
<td>Elastic liver enzymes E&gt;A Hyperlipidaemia A&gt;E</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>EBCTCG 2015</td>
<td></td>
<td></td>
<td>31920</td>
<td></td>
<td>10 y. gain recurrence rate 5 y. Al vs. 5 y. Tam 3.6%, p&lt;0.0001</td>
<td></td>
<td></td>
<td>Randomization for Celecoxib cancelled</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 y. gain OS 5 y. Al vs. 5 y. Tam 2.1%, p&lt;0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 y. gain OS 5 y. Al vs. 2-3 y. Tam → Al to y. 5 0.7%, p&lt;0.045</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 y. gain OS 5 y. Al vs. 2-3 y. Tam → Al to y. 5 1.1%, p&lt;0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 y. gain OS 2-3 y. Tam → Al to y. 5 1.5%, p&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.

5 Years of Aromatase Inhibitor versus Tamoxifen to Years 2-3 Followed by AI to year 5


Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.

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


Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.

Upfront Monotherapy: Meta-analyses of DFS and OS

Upfront Sequential Therapy: Meta-analyses of DFS

Upfront Sequential Therapy: Meta-analyses of OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Upfront sequential therapy: Meta-analyses of DFS and OS

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.
Extended Endocrine Therapies
Gnant M. et al., SABCS, 2016 (S1-06, Discussion)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA-17</td>
<td>TAM</td>
<td>0-6</td>
</tr>
<tr>
<td>NSABP-B33</td>
<td>TAM</td>
<td>0-8</td>
</tr>
<tr>
<td>ABCSG-6a</td>
<td>TAM</td>
<td>0-8</td>
</tr>
<tr>
<td>NSABP-B42</td>
<td>AI</td>
<td>0-8</td>
</tr>
<tr>
<td>MA-17R</td>
<td>AI</td>
<td>0-8</td>
</tr>
<tr>
<td>ABCSG-16</td>
<td>Tam</td>
<td>0-8</td>
</tr>
<tr>
<td>DATA</td>
<td>Tam</td>
<td>0-8</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Tam</td>
<td>0-8</td>
</tr>
<tr>
<td>SOLE</td>
<td>AI</td>
<td>0-8</td>
</tr>
</tbody>
</table>

**Notes:**
- TAM: Tamoxifen
- AI: Aromatase Inhibitor
- Let: Letrozole
- Exe: Exemestane
- Placebo

**Studies:**
- NSABP-B33
- ABCSG-6a
- NSABP-B42
- MA-17R
- ABCSG-16
- DATA
- IDEAL
- SOLE

**Additional Information:**
- nsABP-B33
- ABCSG-6a
- nsABP-B42
- MA-17R
- ABCSG-16
- DATA
- IDEAL
- SOLE

**References:**
- Gnatt M. et al., SABCS, 2016 (S1-06, Discussion)
# Aromatase Inhibitors in Adjuvant Therapy

## Overview over Published Trials: Extended Therapy I

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

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Patient number</th>
<th>Population</th>
<th>Upfront therapy</th>
<th>Trial Arms</th>
<th>Reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATER</td>
<td>Zdenkowski 2016</td>
<td>360</td>
<td>Postm.</td>
<td>≥ 4 years of endocrine therapy (11.7% Al, 50.3% Tam, 38.0% other)</td>
<td>5 y. letrozole vs. observation</td>
<td>Breast cancer recurrence difference: 8.4% (3.8%-13.0%), p=0.0004</td>
</tr>
<tr>
<td>MA17R</td>
<td>Goss 2016</td>
<td>1918</td>
<td>Postm.</td>
<td>5 years of any other AI with or without prior tamoxifen</td>
<td>Letrozole vs. placebo</td>
<td>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)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Blok 2016</td>
<td>1824</td>
<td>Postm.</td>
<td>5 years of tamoxifen, Al or tamoxifen → Al</td>
<td>Letrozole 2.5 vs. 5 years</td>
<td>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)</td>
</tr>
<tr>
<td>DATA</td>
<td>Tjan-Heijnen 2016</td>
<td>1912</td>
<td>Postm.</td>
<td>Tamoxifen 2-3 years</td>
<td>Anastrozole 6 vs. 3 years</td>
<td>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)</td>
</tr>
</tbody>
</table>
| NSABP B-42 | Mamounas 2016 | 3923 | Postm. | Al or tamoxifen → Al 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

- 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

- **Premenopausal**
  - Tamoxifen
  - Exemestan, Tam & GnRH

- **Postmenopausal**
  - Tamoxifen
  - Letrozol (MA.17)

- **Adjuvant Year 0-5**
  - Tamoxifen
  - AI
  - Tam
  - AI
  - TAM

- **EAT Year 6-10**
  - Tamoxifen
  - Letrozol (MA.17)
  - AI

- **Carry over effect > 10**
  - Letrozol (MA.17R)
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

References:

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

No further information

References:

Adjuvant Endocrine Therapy (5/29)

No further information

References:

Adjuvant Endocrine Therapy (6/29)

No further information

References:

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

No further information

References:


10. Gnant M. The bumpy road to extending adjuvant therapy
Discussant General Session 1, Dec. 7th, SABCS 2016, https://watch.ondemand.org/OnlinePlayer/228
References:

GnRHa alone 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 +/-


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

No further information

References:

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 first 5 yrs. 1a A +


3. 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


Further references for patient care/ adherence and side effects


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

No further information

References:

2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy  


5 years Tamoxifen after 5 years Tamoxifen (in case of higher risk)  


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 tolerability of the AI  

1b  B  +

low risk, poor tolerability of the AI  

1b  B  -

letrozole treatment after 5 years of adjuvant endocrine therapy; results of the randomized phase III IDEAL trial (BOOG 2006-05). 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-04


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

No further information

References:

See chapter 25 Gynecological problems
TEXT /SOFT Joint Analysis (12/29)

No further information

References:


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

No further information

References:

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

No further information

References:

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

References:

1. Grey RG, Rea K, Handley K et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer J Clin Oncol 31, 2013(suppl; abstract 5)
Upfront therapies - Overview (16/29)

No further information

References:

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

No further information

References:

6. Duffy S. Gynecological adverse events including hysterectomy with anastrozole tamoxifen: Data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. J Clin Oncol 2005;23(Suppl.):58S, Abs 723.
5 Years of Aromatase Inhibitor versus 5 Years of Tamoxifen (18/29)

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

Extended Endocrine Therapies (25/29)

No further information

References:

1. Gnant M. et al., SABCS, 2016 (S1-06, Discussion)
Aromatase Inhibitors in Adjuvant Therapy Overview over Published Trials: Extended Therapy I (26/29)

No further information

References:


comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-03


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
Adjuvant Cytotoxic and Targeted Therapy
Adjuvant Cytotoxic and Targeted Therapy

- **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
Subtype-specific
General Systemic Strategies

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”**
- Convectionally 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**
- Convectionally dosed AT-based chemotherapy
  - ++
- Dose dense & escalated
  - +
- Neoadjuvant platinum containing chemotherapy
  - +
### Adjuvant Chemotherapy without Trastuzumab: Overview

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracycline / taxane based chemotherapy</td>
<td>1a A ++</td>
</tr>
<tr>
<td>If anthracyclines cannot be given</td>
<td></td>
</tr>
<tr>
<td>Docetaxel plus cyclophosphamide</td>
<td>1b B +</td>
</tr>
<tr>
<td>Paclitaxel mono weekly</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>CMF</td>
<td>1a A +/-</td>
</tr>
<tr>
<td>Dose-dense in case of high tumor burden</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Low dose maintenance chemo</td>
<td>1b B -</td>
</tr>
</tbody>
</table>
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

**Anthracycline / taxane based regimen**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
<th>Oxford</th>
<th>LoE</th>
<th>AGO</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>*EC → P_w</td>
<td>$E_{90}C$ q3w x 4 $→ P_{80}$ qw1 x 12</td>
<td>1b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>AC → P_w</td>
<td>$A_{60}C$ q3w x 4 $→ P_{80}$ qw1 x 12</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>AC → D</td>
<td>$A_{60}C$ q3w x 4 $→ D_{100}$ qw3 x 4</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>*EC → D</td>
<td>$E_{90}C$ q3w x 4 $→ D_{100}$ qw3 x 4</td>
<td>1b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>DAC</td>
<td>$D_{75}A_{50}C$ q3w x 6</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

**Anthracycline-free regimen**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
<th>Oxford</th>
<th>LoE</th>
<th>AGO</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>$D_{75}C_{600}$ x4</td>
<td>1b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pac mono</td>
<td>$P_{80}$ q1w x 12</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>CMF</td>
<td></td>
<td>1a</td>
<td>A</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

* Extrapolated from doxorubicin trials
## Dose-dense and / or Dose-escalated Adjuvant Chemotherapy in Case of High Tumor Burden

### Dose-dense regimen

- *EC q3w x 4 → Pac q1w x 12
- AC q3w x 4 → Pac q1w x 12
- AC q2w x 4 → Pac q2w x 4
- EC q2w x 4 → Pac q2w x 4
- EC q2w x 4 → Pac q1w x 12

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

- E-Pac-C q2w

### Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th></th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>*EC q3w x 4 → Pac q1w x 12</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>AC q3w x 4 → Pac q1w x 12</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>AC q2w x 4 → Pac q2w x 4</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>EC q2w x 4 → Pac q2w x 4</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>EC q2w x 4 → Pac q1w x 12</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>E-Pac-C q2w</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>

* Extrapolated from doxorubicin trials
Adjuvant Chemotherapy
Other Drugs

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a B +/-</td>
<td>Capecitabine containing regimen in TNBC</td>
</tr>
<tr>
<td>5 D +/-</td>
<td>Platinum containing regimen in TNBC</td>
</tr>
<tr>
<td>1b A - -</td>
<td>5- Fluorouracile added to EC/AC</td>
</tr>
</tbody>
</table>
Adjuvant Treatment with Trastuzumab I

- Node-positive disease
  - > 10 mm
  - > 5–10 mm
  - ≤ 5 mm

- Node-negative disease
  (whenever chemotherapy is considered as adequate)
  - > 10 mm
  - > 5–10 mm
  - ≤ 5 mm

Oxford / AGO
LoE / GR

1a A ++
1a A ++
2b B +
2b B +/-
Adjuvant Treatment with Trastuzumab II

Start of treatment

- Simultaneously with taxanes
- Sequentially up to 3 months after chemotherapy

Duration

- For 1 year
- For 2 years
- For 0.5 years
Before start of trastuzumab
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

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
Adjuvant Treatment with Trastuzumab: Schedules

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

Radiotherapy concurrent with Trastuzumab  
2b B +

* Study participation recommended
Adjuvant Therapy with Other Targeted Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>(delayed adjuvant treatment)</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1b</td>
<td>B</td>
<td>--</td>
</tr>
</tbody>
</table>
Adjuvant Cytotoxic and Targeted Therapy (2/13)

No further information

No references
Subtype-specific General Systemic Strategies (3/13)

No further information:

References:

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%


Statement: If anthracyclines cannot be given - Docetaxel plus cyclophosphamide (1b B +)
Vote result of the AGO recommendation: 100%

Statement: If anthracyclines cannot be given - Paclitaxel mono weekly (1b B +/-)
Vote result of the AGO recommendation: 100%


Statement: If anthracyclines cannot be given - CMF (1a A +/-)
Vote result of the AGO recommendation: 100%


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


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

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%


Statement: Anthracycline/ taxane based regimen  
*AC → Pw A60Cq3w x 4 → P80qw1 x 12 (1b A++)*  
Vote result of the AGO recommendation: 100%


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 +/-


Statement: Anthracycline-free regimen
DC  D75 C600 x4 (1b B +)
Vote result of the AGO recommendation: 100%


Statement: Anthracycline-free regimen
Pac mono  80 mg q1w x 4-6 (1b B +/-)
Vote result of the AGO recommendation: 100%

Statement: Anthracycline-free regimen
CMF 600/40/600 mg q3w x 6 (1a A +/-)
Vote result of the AGO recommendation: 100%

**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%


**Statement:** Dose-dense regimen

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

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


**Statement:** Dose-dense regimen

EC q3w / Pac q2w (1b A+)
EC q2w / Pac q1w (1b B+)

Vote result of the AGO recommendation: 100%

Statement: Dose-dense and dose-escalated regimen (N ≥ 4+)
E-Pac-C q2w (1b A ++)
Vote result of the AGO recommendation: 100%


Negative Trial

**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%


**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%

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%


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

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


**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%


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 --


Adjuvant Trastuzumab – Cardiac Monitoring for CHF (11/13)

Further information and references:

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


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%


Statement: P q1w12 without A in pT ≤ 3 cm pN0 (2b B +)
Vote result of the AGO recommendation: 100%


Statement: with docetaxel and carboplatin (1b A +)
Vote result of the AGO recommendation: 100%


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%

Adjuvant Therapy with Other Agents (13/13)

Further information and references:

Statement: with Lapatinib (1b\(^a\) B -)
Delayed adjuvant treatment (1b B -)
Vote result of the AGO recommendation: 100%


Statement: with Lapatinib + Trastuzumab (1b\(^a\) B -)
Vote result of the AGO recommendation: 100%

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%


Statement: Neratinib after adjuvant trastuzumab (1bª B +/−)
Vote result of the AGO recommendation:

Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Versions 2002–2016:**
  Bauerfeind / Blohmer / Costa / Dall / Fersis / Friedrich / Göhring / Harbeck / Heinrich / Huober / Jackisch / Kaufmann / Liedtke / Loibl / Lux / von Minckwitz / Müller / Nitz / Schneeweiss / Schütz / Solomayer / Untch

- **Version 2017:**
  Loibl / Müller
Subtype-specific General Systemic Strategies

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
## Neoadjuvant Systemic Chemotherapy Clinical Benefit

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
</table>

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

* Study participation recommended
Neoadjuvant Systemic Chemotherapy Indications

- Inflammatory breast cancer
  - Oxford / AGO LoE / GR: 2b B ++

- Inoperable breast cancer
  - Oxford / AGO LoE / GR: 1c A ++

- Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
  - Oxford / AGO LoE / GR: 1b B +

- If similar postoperative adjuvant chemotherapy is indicated
  - Oxford / AGO LoE / GR: 1b A +
# Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
<thead>
<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>cT1 / cT2 tumors o. N0 o. G3</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Negative ER and PgR status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Positive HER2 status</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Non-lobular tumor type</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Early clinical response</td>
<td>B</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>
### Neoadjuvant Systemic Therapy Response Prediction II

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE\textsubscript{2009}</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigene signatures</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumor infiltrating lymphocytes*</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>gBRCA in TNBC</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

*defined as dense lymphocytic infiltration of inner peritumoral stroma outside of the invasion front (>50% lymphocytes of stromal area).*
Neoadjuvant Systemic Chemotherapy
Recommended Regimens and Schedules

- Standard protocols used in the adjuvant setting with a duration of at least 18 weeks
  
  - AC or EC → D q3w or P q1w
  - DAC
  - Taxane followed by anthracycline
  - Dose-dense regimen (e.g. E-P-CMF, E-P-C)
  - Platinum in TNBC (irrespective of BRCA status)
  - Nab-Paclitaxel weekly instead of Paclitaxel weekly

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>2b A ++</td>
<td></td>
</tr>
<tr>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>1b B +*</td>
<td></td>
</tr>
<tr>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>1b B +/-</td>
<td></td>
</tr>
</tbody>
</table>

*Study participation recommended
## Potential Carboplatin Containing Regimens in the Neoadjuvant Setting

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Regimen</th>
<th>pCR rate</th>
<th>3-yr EFS rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sikov WM, et al.</td>
<td>CALGB 40603</td>
<td>Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 6 q3w x4 – dd AC q2w x4</td>
<td>TNBC ± Cb: 54% vs 41% (ypT0/is ypN0)</td>
<td>TNBC ± Cb: 72% vs. 77% (HR 0.84 (95%CI 0.58-1.22))</td>
</tr>
<tr>
<td>JCO 2015, SABCS 2015</td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Minckwitz G, et al.</td>
<td>Gepar Sixto</td>
<td>NPLD 20mg/m² qw x18 + Paclitaxel 80mg/m² qw x18 + Carboplatin AUC 1.5 qw x18 + Bev 15 mg/kg q3w x6</td>
<td>TNBC ± Cb: 53% vs. 37% (ypT0 ypN0)</td>
<td>TNBC ± Cb: 76% vs. 86% (HR 0.56 (95%CI 0.33-0.96))</td>
</tr>
<tr>
<td>Lancet Oncol 2014, SABCS 2015</td>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ando M, et al.</td>
<td>Phase II</td>
<td>Paclitaxel 80mg/m² qw x12 + Carboplatin AUC 5 q3w x4 – FEC q3w x4</td>
<td>TNBC ± Cb: 61% vs. 26%</td>
<td></td>
</tr>
<tr>
<td>BCRT 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Chemotherapy
Recommended Methods of Monitoring of Response

<table>
<thead>
<tr>
<th>Method</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast ultrasound</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Palpation</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Mammography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>MRI</td>
<td>2b B +</td>
</tr>
<tr>
<td>PET(-CT)*</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Clip tumor region</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Clip positive lymph node</td>
<td>3 C +/-</td>
</tr>
</tbody>
</table>

* Study participation recommended
## Neoadjuvant Targeted Therapy in HER2 Positive Tumors

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab in combination with chemotherapy</td>
<td>1b</td>
<td>A++</td>
<td>++</td>
</tr>
<tr>
<td>Pertuzumab + Trastuzumab in combination with chemotherapy</td>
<td>2b</td>
<td>B++</td>
<td>++</td>
</tr>
<tr>
<td>Lapatinib in combination with chemotherapy</td>
<td>1a</td>
<td>B-</td>
<td></td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab in combination with chemotherapy</td>
<td>1a</td>
<td>B+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Two anti-HER2 agents without chemotherapy</td>
<td>2b</td>
<td>B+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Oxford / AGO LoE / GR
Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Bevacizumab in combination with chemotherapy

- In hormone receptor positive BC
- In TNBC

Oxford / AGO
LoE / GR

1b  B  -
1b  B  +/-
Neoadjuvant Systemic Therapy Procedures in Case of Early Response

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  +
Neoadjuvant Systemic Therapy
Procedures in Case of No Early Response

In case of no change:

- Completion of NST, followed by surgery
- Continuation of NST with non cross-resistant regimen
  - AC or EC x 4 → D x 4 or Pw x 12
  - DAC x 2 → NX x 4

In case of progressive disease:

- Stop of NST and surgery or radiotherapy
- Additional adjuvant chemotherapy with non cross-resistant regimen

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Level</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion of NST, followed by surgery</td>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Continuation of NST with non cross-resistant</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC or EC x 4 → D x 4 or Pw x 12</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>DAC x 2 → NX x 4</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Stop of NST and surgery or radiotherapy</td>
<td>4</td>
<td>D</td>
<td>++*</td>
</tr>
<tr>
<td>Additional adjuvant chemotherapy with non</td>
<td>4</td>
<td>D</td>
<td>+/-*</td>
</tr>
<tr>
<td>cross-resistant regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Study participation recommended
Local / Regional Procedure after Neoadjuvant Therapy

- Mark previous tumor region  
- Surgery  
- Microscopically clear margins  
- Tumor resection according to imaging result

Oxford / AGO LoE / GR

- Mark previous tumor region  
  
- Surgery  
  
- Microscopically clear margins  
  
- Tumor resection according to imaging result  

5 D ++  
2b C ++  
5 D ++  
3b C +
## Axillary Intervention Before or After NACT

### SLNB before or after NACT in cN0

<table>
<thead>
<tr>
<th>SLNB before NACT</th>
<th>SLNB after NACT</th>
<th>cN-Status (before NST)</th>
<th>pN-Status (before NST)</th>
<th>Surgical Procedure (after NST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB after NACT</td>
<td></td>
<td>cN0</td>
<td>pN0(sn)</td>
<td>nihil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cN0</td>
<td>pN+(sn)</td>
<td>Re-SLNB alone ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cN0</td>
<td>pN+(sn)</td>
<td>Re-SLNB alone ALND Axilla XRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cN0</td>
<td>not done</td>
<td>SLNB alone ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cN+</td>
<td>pN+ (CNB/FNA)</td>
<td>SLNB alone* ALND ALND</td>
</tr>
</tbody>
</table>

### Further surgical procedures depending on SLNB status

<table>
<thead>
<tr>
<th>cN-Status (before NST)</th>
<th>pN-Status (before NST)</th>
<th>cN-Status (after NST)</th>
<th>Surgical Procedure (after NST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>ycN0</td>
<td>nihil</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>Re-SLNB alone ALND</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>Re-SLNB alone ALND Axilla XRT</td>
</tr>
<tr>
<td>cN0</td>
<td>not done</td>
<td>ycN0</td>
<td>SLNB alone ALND</td>
</tr>
<tr>
<td>cN+</td>
<td>pN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SLNB alone* ALND ALND</td>
</tr>
</tbody>
</table>

### References

Further surgical procedures depending on SLNB status.
# Neoadjuvant Systemic Therapy

## Indications for Mastectomy

- Positive margins after repeated excisions
  - Oxford / AGO LoE / GR: 3b C ++
- Radiotherapy not feasible
  - Oxford / AGO LoE / GR: 5 D ++
- In case of clinical complete response
  - Inflammatory breast cancer
    - Oxford / AGO LoE / GR: 2b C +
    - In case of pCR: +/-
  - Multicentric lesions
    - Oxford / AGO LoE / GR: 2b C +/-
  - cT4a-c breast cancer
    - Oxford / AGO LoE / GR: 2b B +/-
Neoadjuvant Systemic Therapy
Timing of Surgery and Radiotherapy

- **Surgery**
  - After the nadir of the leucocyte count
    (2 to 4 weeks after last course of chemotherapy)
- **Radiotherapy** within 2–3 weeks after surgery BCS

Oxford / AGO
LoE / GR

4  C  ++

2b  B  ++
### Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

<table>
<thead>
<tr>
<th><strong>Guidelines</strong></th>
<th><strong>Oxford / AGO LoE / GR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine treatment in endocrine responsive disease</strong></td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>Complete trastuzumab treatment for 1 year in HER2-positive disease</strong></td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>Complete pertuzumab treatment for 1 year in HER2-positive disease</strong></td>
<td>3 C -</td>
</tr>
<tr>
<td><strong>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)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2bα B +/-</td>
</tr>
<tr>
<td></td>
<td>3 C -</td>
</tr>
<tr>
<td></td>
<td>5 D +</td>
</tr>
<tr>
<td><strong>Capecitabine adjuvant in TNBC</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Further chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Experimental therapies in clinical trials</strong></td>
<td></td>
</tr>
</tbody>
</table>
# Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

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

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

- **Concurrent chemo-endocrine therapy**

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

| Oxford / AGO LoE / GR | 2a B + | 1b A + | 1a A + | 2b B +/- | 5 C + | 2b C + | 1b C +/- | 1b A - | 1b B + |

Optimal duration of neoadjuvant endocrine therapy is unknown
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)
Neoadjuvant (Primary) Systemic Therapy (2/20 and 3/20)

Further information 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


Pathological complete response is associated with improved survival in particular subgroups (HR+/HER2neg/Grade3, HER2-pos and TNBC)

Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Can achieve operability in primary inoperable tumors
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Improved options for breast conserving surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Allows individualization of therapy according to mid-course treatment effect
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Allows individualization of post-neoadjuvant treatment
Abstimmungsergebnis der AGO-Empfehlungen: 2/7/20/1/0 (2016)

Neoadjuvant Systemic Chemotherapy Indications (5/20)

Further information and references:

Inflammatory breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Inoperable breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

If similar postoperative adjuvant chemotherapy is indicated
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Neoadjuvant Systemic Chemotherapy Response Prediction I (6/20)

Further information and references:

Young age
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


cT1 / cT2 tumors o. N0 o. G3
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Negative ER and PgR status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Triple negative breast cancer (TNBC)**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Positive HER2 status**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**Non-lobular tumor type**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**Early clinical response**

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

Further information and references:

Multigene signature
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


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


**Tumour infiltrating lymphocytes**

Abstimmungsergebnis der AGO-Empfehlungen: 0/15/10/0/0 (2016)


**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


**gBRCA mutation**
Abstimmungsergebnis der AGO-Empfehlungen:

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


AC or EC → D q3w or P q1w
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


DAC
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Taxane followed by anthracycline sequence
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


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


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

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.

Nab-Paclitaxel weekly instead of Paclitaxel weekly
Abstimmungsergebnis der AGO-Empfehlungen

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

Further information and references:


Breast ultrasound
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Palpation
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Mammography
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

**MRI**

Abstimmungsergebnis der AGO-Empfehlungen: 45/0


**PET(-CT)**

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Clip tumour region
Abstimmungsergebnis der AGO-Empfehlungen: 45/0
Neoadjuvant Targeted Therapy in HER2 Positive Tumors (11/20)

Further information and references:

Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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


Lapatinib in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Lapatinib + Trastuzumab in combination with chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Pertuzumab + Trastuzumab in combination with chemotherapy

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

Two anti-HER2 agents without chemotherapy

Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

1. Rimawi MF, et al. SABCS 2014 (S6-02)
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-


Bevacizumab in combination with chemotherapy in TNBC
Abstimmungsergebnis der AGO-Empfehlungen: 2+-/-, 13+-/-, 9-


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


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

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


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

Abstimmungsergebnis der AGO-Empfehlungen: 45/0


In case of progressive disease:
Stop of NST and immediate surgery or radiotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Additional adjuvant chemotherapy with non-cross-resistant regimen
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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


Surgery
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Microscopically clear margins
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Tumor resection according to imaging result
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Sentinel node biopsy (see chapter “Surgery”)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

Further information and references:

Positive margins after repeated excisions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Radiotherapy not feasible
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


In case of clinical complete response:
Inflammatory breast cancer in case of pCR
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Multicentric lesions
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


cT4a-c breast cancer
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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


Radiotherapy after surgery 2–3 weeks after surgery BCS
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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)


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

Further chemotherapy

Experimental therapies in clinical trials

Otherwise no references
Neoadjuvant Endocrine Therapy (20/20)

Further information and references:

Postmenopausal patients:
Who are inoperable and can / will not receive chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Optimizes the option for breast conserving therapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Aromatase inhibitors (for > 3 months)
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


AI and fulvestrant


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


Prognostic factors during/after NST: quantitative ER-expression, level of Ki-67, N status, T status
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

- Radiotherapy of the affected breast

- Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)

- Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)

- 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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
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<sub>OS</sub>=0.8; p=0.042)

➢ 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

<table>
<thead>
<tr>
<th>@10 yrs (95% C.I.)</th>
<th>Tamoxifen</th>
<th>Tamoxifen plus Radiotherapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence free (Δ=8%)</td>
<td>90% (85%-93%)</td>
<td>98% (96%-99%)</td>
<td>HR=0.18 (95% CI, 0.07 to 0.42; P &lt; .001)</td>
</tr>
<tr>
<td>Mastectomy-free</td>
<td>96% (93% - 98%)</td>
<td>98% (96% - 99%)</td>
<td>HR=0.50 (95% CI, 0.17 to 1.48; n.s.)</td>
</tr>
<tr>
<td>Distant metastasis-free</td>
<td>95% (91% - 97%)</td>
<td>95% (92% - 97%)</td>
<td>HR=1.20 (95% CI, 0.63 to 2.32; n.s)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>66% (61% - 71%)</td>
<td>67% (62% - 72%)</td>
<td>HR=0.95 (95% CI, 0.77 to 1.18; n.s.)</td>
</tr>
</tbody>
</table>

Hughes KE et al J Clin Oncol 2013; 31:2382-2387
Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation

- **Boost-RT (improves local control, no survival benefit)**
  - Premenopausal
  - Postmenopausal, if >T1, G3, HER2-positive, triple negative, EIC (at least 1 factor)

- **Intraoperative irradiation (intraop. APBI)**
  - As boost-irradiation followed by WBI
  - As sole radiotherapy modality (IORT 50 kV, IOERT)**
    - >50 years**
    - >70 years**

- **Postoperative partial breast irradiation as sole radiotherapy modality (APBI)**
  - Interstitial brachytherapy
    - >70 years**
  - Intracavity balloon technique
  - IMRT***

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Boost-RT</th>
<th>Premenopausal</th>
<th>Postmenopausal, if &gt;T1, G3, HER2-positive, triple negative, EIC (at least 1 factor)</th>
<th>Intraoperative irradiation (intraop. APBI)</th>
<th>As boost-irradiation followed by WBI</th>
<th>As sole radiotherapy modality (IORT 50 kV, IOERT)**</th>
<th>Postoperative partial breast irradiation as sole radiotherapy modality (APBI)</th>
<th>Interstitial brachytherapy</th>
<th>Intracavity balloon technique</th>
<th>IMRT***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>B</td>
<td>++</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td>1a</td>
<td>A</td>
<td>+/-*</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
<td>2a</td>
<td>B</td>
<td>+</td>
<td>1b</td>
<td>B</td>
<td>+/-*</td>
<td>1b</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>+</td>
<td>1a</td>
<td>A</td>
<td>+</td>
<td>1b</td>
<td>B</td>
<td>-</td>
<td>2b</td>
</tr>
</tbody>
</table>

* Study participation recommended; **only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery; ***no long term data
## EORTC 22881-10882: Boost vs no Boost
(Endpoint: Ipsilateral Breast Recurrence)

<table>
<thead>
<tr>
<th></th>
<th>Boost (n=2,661)</th>
<th>No boost (n=2,657)</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td>59.7% (56.3–63.0)</td>
<td>61.1% (57.6–64.3)</td>
<td>HR 1.05 (0.92–1.19) n.s.</td>
</tr>
<tr>
<td><strong>Cumulative Risk of Ipsilateral Breast Tumor Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>12.0% (9.8–14.4)</td>
<td>16.4% (14.1–18.8)</td>
<td>HR=0.65 (0.52–0.81); p&lt;0.0001</td>
</tr>
<tr>
<td>≤40 years</td>
<td>24.4% (14.9–33.8)</td>
<td>36.0% (25.8–46.2)</td>
<td>HR=0.56 (0.34–0.92); p=0.003</td>
</tr>
<tr>
<td>41–50 years</td>
<td>13.5% (9.5–17.5)</td>
<td>19.4% (14.7–24.1%)</td>
<td>HR=0.66 (0.45–0.98); p=0.007</td>
</tr>
<tr>
<td>51–60 years</td>
<td>10.3% (6.3–14.3)</td>
<td>13.2% (9.8–16.7)</td>
<td>HR=0.69 (0.46–1.04); p=0.020</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>9.7% (5.0–14.4)</td>
<td>12.7% (7.4–18.0)</td>
<td>HR=0.66 (0.42–1.04); p=0.019</td>
</tr>
</tbody>
</table>

(Median F/U 17.2 y)

### EORTC 22881-10882: Boost vs no Boost (Endpoint: Any First Recurrence)

#### Overall Survival

<table>
<thead>
<tr>
<th>@15 yrs/20 yrs (95% C.I.)</th>
<th>Boost (n=2,661)</th>
<th>No boost (n=2,657)</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (Δ = -1.4%)</td>
<td>59.7% (56.3–63.0)</td>
<td>61.1% (57.6–64.3)</td>
<td>HR 1.05 (0.92–1.19) n.s.</td>
</tr>
</tbody>
</table>

#### Cumulative Risk of Any First Recurrence

<table>
<thead>
<tr>
<th>All patients (Δ ≥ 4%)</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
</tr>
</thead>
<tbody>
<tr>
<td>@15y</td>
<td>28.1%</td>
<td>32.8%</td>
<td>32.1%</td>
<td>38.7%</td>
<td>HR=0.92 (0.81-1.04), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@20y</td>
<td>32.8%</td>
<td>38.7%</td>
<td>38.7%</td>
<td>44.2%</td>
<td>HR=0.80 (0.56-1.15) , n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40 years (Δ &gt; 6%)</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
</tr>
<tr>
<td>@15y</td>
<td>41.5%</td>
<td>49.5%</td>
<td>48.1%</td>
<td>56.8%</td>
<td>HR=0.80 (0.56-1.15) , n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@20y</td>
<td>49.5%</td>
<td>56.8%</td>
<td>56.8%</td>
<td>64.2%</td>
<td>HR=0.91 (0.71-1.16), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41–50 years</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@20y</td>
<td>38.6%</td>
<td>44.2%</td>
<td>44.2%</td>
<td>52.8%</td>
<td>HR=0.96 (0.76-1.21), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51–60 years</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
<td>@15y</td>
<td>@20y</td>
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<td>@20y</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall

<table>
<thead>
<tr>
<th>Indications</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 tumor infiltrated lymph nodes (Lnn.)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. (high risk)</td>
<td>1a A +</td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. (low risk*)</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>T3 / T4</td>
<td>1a A ++</td>
</tr>
<tr>
<td>pT3 pN0 R0 (and no additional risk factors)</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>If R0 is impossible to reach (for invasive tumor)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>In young pts with high risk features</td>
<td>2b B ++</td>
</tr>
<tr>
<td>After neoadjuvant chemotherapy (NACT) based on the initial stage prior to</td>
<td>2a B +</td>
</tr>
<tr>
<td>NACT (cN+ (CNB/FNA), cT3/4a-d)</td>
<td></td>
</tr>
<tr>
<td>Omission of RT if ypT0 ypN0 after NACT**</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>

The indications for PMRT and regional RT are independent of adjuvant systemic treatment 1a A

*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

## PMRT

<table>
<thead>
<tr>
<th>PMRT can be omitted</th>
<th>PMRT to be discussed</th>
<th>PMRT recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>LoE 3b B AGO +</td>
<td>LoE 3b B AGO +/-</td>
<td>LoE 3b B AGO +</td>
</tr>
</tbody>
</table>

**ER pos, G1, HER2 neg, pT1 (at least 3 criteria present)**

- **Kyndi et al. 2013**

**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**

- **Truong et al. 2005**

**<45 y. AND (ER neg. OR >25% pos. ax. Lnn in case of axillary dissection OR medial tumor location)**

**<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
Radiotherapy of the Axilla

- Tumor residuals after axillary dissection
  - Oxford / AGO LoE / GR: 5 D ++
- Sentinel node negative
  - Oxford / AGO LoE / GR: 1b B - -
- Axillary dissection not indicated e.g. cN0, SLN pos. (see chapter surgery)
  - Oxford / AGO LoE / GR: 2a B -
- Extracapsular tumor spread (ECS)
  - Oxford / AGO LoE / GR: 2b B -
- Axillary micrometastases or isolated cells found in regional lymph nodes
  - Oxford / AGO LoE / GR: 1b B - -
Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

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

- If BCT and ACOSOG Z011-criteria fulfilled
  - No axillary treatment
- If mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled
  - No further axillary treatment

- If BCT and ACOSOG Z011-criteria not met
- If mastectomy: PMRT and ACOSOG Z0011-criteria not met, or PMRT not planned

>=3 pos. SLN:

- Axillary dissection
- Radiotherapy of the axilla

*Study participation recommended
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)

RT to supra-/infraclavicular lymphatic regions

- ≥pN2a or level III involved
- 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)
- pN0 high risk** with central or medial tumors
  ** premenopausal and G2-3 and ER/PgR-negative
- After NACT/NAT (indications as for PMRT)
  AGO¹
- After NACT/NAT if cN+ (CNB/FNA) (ind. as for PMRT)
  DEGRO¹

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A ++</td>
<td></td>
</tr>
<tr>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td>2a B +/-</td>
<td></td>
</tr>
<tr>
<td>2b B +/-</td>
<td></td>
</tr>
</tbody>
</table>

¹ Different interpretation of published data by AGO and DEGRO
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

Internal mammaria lymph node region (IMN)

- **pN0 high risk*** with central or medial tumor
  ***premenopausal and G2-3 and ER/PgR-negative
- **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)
- **pN2a high risk**
  **G2-3 or ER/PgR-negative
- **pN1b-c, pN2c, pN3b
- IMC-RT, if cardiac risk factors are present
  or if trastuzumab is given
- After NACT/NAT (indications as for PMRT) AGO
- After NACT/NAT if cN+ (CNB/FNA) (ind. acc. PMRT) DEGRO

1 Different interpretation of published data by AGO and DEGRO
Fractionation of Radiotherapy in Case of Radiotherapy of the Regional Lymph Nodes

- Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)

- Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)
Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(median follow-up 10.9 yrs)

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

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013
Concomitant Use of Systemic Therapy with Radiotherapy

- **Trastuzumab*** concurrent with radiotherapy  
  2b  B  +

- **Tamoxifen** concurrent with radiotherapy  
  2b  B  +

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

*In HER2 pos. tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT
Interaction between Smoking and Risk of Irradiation-induced Side Effects

- Enhanced risk of lung cancer secondary to breast cancer radiotherapy in smokers
- Inform patients about the risk
- Recommend to stop smoking

Oxford / AGO LoE / GR
1a A

++
++
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.


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

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.


Guidelines and Opinions (4/20)

No further information

References:


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 surviv-
al, and the biology of the tumor dictates the rate of IBTR, not the length of life.

References:


15. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.


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)


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:


**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:*

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:


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


Boost-RT in premenopausal p. (LoE 1b A AGO++)
Boost-RT in postmenopausal p. (LoE 2b B AGO+)

Intraoperative irradiation (IORT/IOERT)
As boost-irradiation followed by WBI (LoE 2a B AGO+)


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+-)


>70 yrs LoE 1a A AGO+


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


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


Intracavity balloon technique (LoE 1b B AGO-)


IMRT (LoE 1b B AGO-*)

2. Livi L¹, Meattini I², Marrazzo L³, Simontacchi G¹, Pallotta S³, Saieva C⁴, Paier F¹, Scotti V¹, De Luca Cardillo C¹, Bastiani P⁵, Orzalesi L⁶, Casella D⁶, Sanchez L⁶, Nori J⁷, Fambrini M⁸, Bianchi S⁹. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015 Jan 17. pii: S0959-8049(15)00002-7.
**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.

*References:*


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.”.


7. NCCN Guidelines for Treatment of Cancer by Site

References according to the statements:

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


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


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


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors) LoE 2b B AGO+/-):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor) (LoE 1a A AGO++):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features (LoE 2b B AGO++):


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+):


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

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


Further references:

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


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

Radiotherapy of the Axilla (13/20)

Further 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:

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 Krebgesellschaft e.V. und Deutschen Krebshilfe e.V.

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

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


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

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


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+/-)


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


1-2 pos SLN: BCT: radiotherapy of the axilla (LoE 1b B, AGO +/−)


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

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:

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

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


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

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%).

References:


References related to the statements:

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


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


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


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


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


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

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

No further information

References:

Internal mammaria lymph node region (IMN)

RT to Internal mammaria lymph node region (IMC) if pN0 high risk with central/medial tumors LoE 1b


RT to Internal mammaria lymph node region (IMN) if pN1-pN2 and HR positive in patients who had systemic chemotherapy 

LoE 1b° B; AGO+


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

No further information

References:

Multivariate Analysis of Overall Survival: 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*

**References:**

- Trastuzumab* concurrent with radiotherapy (LoE2b B AGO+) (*in HER2 pos tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT)


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


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


Other compounds (bevacizumab)

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

No further information

References:

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Therapy Side Effects
Therapy Side Effects

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

- **Version 2017:**
  Untch / Solomayer
Toxicity Assessment

Acute Toxicity
According to WHO\(^1\) or NCI-CTC\(^2\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Information required</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 none</td>
<td>organs involved</td>
</tr>
<tr>
<td>1 mild</td>
<td>type of toxicity</td>
</tr>
<tr>
<td>2 moderate</td>
<td>time interval after treatment</td>
</tr>
<tr>
<td>3 severe</td>
<td>effect on general health status</td>
</tr>
<tr>
<td>4 life threatening</td>
<td>treatment required</td>
</tr>
<tr>
<td>5 death</td>
<td>recovery achieved</td>
</tr>
</tbody>
</table>

Long-Term Toxicity
No general assessment scale

---

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


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.*
## Cytotoxic Anti-Cancer Drugs
### Acute Toxicity I

<table>
<thead>
<tr>
<th></th>
<th>Haematol. Toxicity</th>
<th>Nausea/Vomit.</th>
<th>Alopecia</th>
<th>Mucositis/Stomatitis</th>
<th>Cardiac Toxicity</th>
<th>Renal Toxicity</th>
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# Cytotoxic Anti-Cancer Drugs

## Acute Toxicity II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allergy</th>
<th>Bladder</th>
<th>Neurotoxicity</th>
<th>Cutane Tox</th>
<th>Diarrhea</th>
<th>Others</th>
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<td>Methotrexate</td>
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<tr>
<td>5-Fluorouracil</td>
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<tr>
<td>Gemcitabine</td>
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<td>Flue-like Synd., Edema</td>
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<tr>
<td>Paclitaxel</td>
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<td>++</td>
<td></td>
<td>+</td>
<td></td>
<td>Myalgia</td>
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<tr>
<td>nab-Paclitaxel</td>
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<td>Docetaxel</td>
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<td>+</td>
<td>++</td>
<td>+</td>
<td>Myalgia, Fluid retention, nails!</td>
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<td>++</td>
<td></td>
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<tr>
<td>Eribulin</td>
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<td>Thrombophlebitis, Obstipation</td>
</tr>
</tbody>
</table>

- **+**: Mild
- **++**: Moderate
- **+++**: Severe

Further Information

References
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

S3 Guideline November 2016
Chemotherapy Induced Peripheral Neuropathy

Prophylaxis

- Non drug
  - Functional training
  - Peripheral compressions therapy

- By drugs

Oxford / AGO LOE / GR

2c C +
2b B +
1b B -
Long-Term Toxicity
Cardiotoxicity

- Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)
- Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity
- Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:
  - Elderly patients
  - Obesity
  - Hypertension
  - Hypercholesterolemia
  - Pre-existing cardiac diseases (incl. borderline LVEF)
  - Diabetes mellitus
- Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)
# Feasibility of Treatment Combinations Considering Toxicities

## Regarding cardiac toxicity
- Trastuzumab simultaneous to radiotherapy
- Trastuzumab simultaneous to epirubicin
- Trastuzumab simultaneous to doxorubicin
- Anthracycline simultaneous to radiotherapy

<table>
<thead>
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<td>B</td>
<td>-</td>
</tr>
<tr>
<td>2c</td>
<td>C</td>
<td>-</td>
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</table>

## Regarding lung and breast fibrosis
- Tamoxifen simultaneous to radiotherapy
- Chemotherapy simultaneous to radiotherapy

<table>
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<th>Grade</th>
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<tbody>
<tr>
<td>3</td>
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<tr>
<td>1b</td>
<td>B</td>
<td>-</td>
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</table>
Side Effects of Trastuzumab/Pertuzumab Algorithm in Case of Cardiac Toxicity

LVEF drop from baseline

LVEF ≥50%
- LVEF drop ≤20% points
  - CONTINUE treatment
- LVEF drop >20% points
  - CONTINUE treatment and repeat LVEF in 3 weeks

LVEF <50%
- LVEF drop <10% points
  - LVEF drop CONFIRMED (LVEF drop ≥10% points and LVEF ≥50%)
    - STOP treatment
  - LVEF drop CONFIRMED (LVEF drop ≥10% points and LVEF <50%)
    - NOT confirmed (LVEF drop <10% points or LVEF ≥50%)
      - LVEF drop CONFIRMED (LVEF drop >20% points and LVEF ≥50%)
        - NOT confirmed (LVEF drop ≥10% points and LVEF ≥50%)
          - RESUME treatment
      - NOT confirmed (LVEF drop ≥10% points and LVEF <50%)
        - CONTINUE treatment and repeat LVEF in 3 weeks
Secondary Malignancies I

- With regard to solid tumors, chemotherapy induced secondary malignancies are rare events 2a
- Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0.2–0.4% within 10–15 years 2a
- Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0.2–1.7% within 8 to 10 years 2a
- PARP-inhibitors are associated with an increased risk of AML and MDS to 0.5–1% 2b
- Radiotherapy increases the risk of leukaemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy 2b
- Tamoxifen approximately doubles the risk for developing endometrial cancer 2b
Secondary Malignancies II (after Radiotherapy)

- The risk of developing secondary cancers is low if modern radiation techniques are applied and should not deter the use of radiotherapy when indicated
  
- Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma (10-15 / 10,000) 5–10 years after treatment
  - Enhanced risk especially among ever smokers

No difference of secondary malignancy between PBI und WBI
Chemotherapy Related Amenorrhea (CRA)

- 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
- Ovarian reserve of women who remain premenopausal after CTX is reduced
- CRA is associated with improved outcome (DFS/OS)

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
(Therapy Related) Fatigue

- Fatigue frequently present in breast cancer patients (30–60%)
- Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue
- Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue
- Physical exercise can improve fatigue
- Diet, Yoga can improve fatigue
- Methylphenidate can improve fatigue

---

Oxford / AGO LoE / GR

- Fatigue: 2a B
- Exclusion of somatic reasons: 1a A ++
- Psycho-social interventions: 1a A ++
- Physical exercise: 1b D +
- Diet, Yoga: 2b B +
- Methylphenidate: 1a D +
Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)  

Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life
Depression is an often reported adverse event in breast cancer patients (20–30%) 

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

Antidepressents have shown to improve depression in breast cancer patients

Regular exercise participation can prevent depression among breast cancer survivors
(Therapy Associated) Cognitive Impairment

- Therapy-related cognitive deficits (chemobrain frequently described (16–75%))
  - Oxford / AGO LoE / GR: 2a B

- Cognitive-behavioral therapy is beneficial for cognitive function
  - Oxford / AGO LoE / GR: 2b B

- Methylphenidate might improve cognitive function in patients with cancer
  - Oxford / AGO LoE / GR: 3a C
# Side-effects and Toxicity of Endocrine Agents

<table>
<thead>
<tr>
<th></th>
<th>Visual Disturbances</th>
<th>Osteoporosis</th>
<th>Cerebro-Vascular Events *</th>
<th>Fracture</th>
<th>Cardiac risk</th>
<th>Cognitive functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERMs</strong></td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><em><em>AI 3rd Gen</em> (Fulvestrant)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>SERD (Fulvestrant)</strong></td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GnRHa</strong></td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Arthralgia</th>
<th>Flush</th>
<th>Dysfunctional Bleeding*</th>
<th>Endometrial Changes</th>
<th>Deep Venous Thrombosis</th>
<th>Lipid Profile Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERMs</strong></td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>AI</strong></td>
<td>(+)</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SERD (Fulvestrant)</strong></td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Goserelin</strong></td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

- 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
Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

  In adjuvant bisphosphonate therapy, ONJ was rare
# Frequent Side Effects of Bone Modifying Agents (BMA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Phase React.</th>
<th>Renal Tox.</th>
<th>Upper GI-SE</th>
<th>Diarrhea</th>
<th>ONJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate 1500 i.v.</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clodronate 1600 p.o.</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 50 mg p.o.</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ibandronate 6 mg i.v.</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 4 mg i.v.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q4w or q12w</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Pamidronate 90 mg i.v.</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate 4 mg i.v. q6m</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Denosumab 120 mg sc q4w 0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
### Key-Toxicities – Antibodies/Antibody-drug-conjugates

<table>
<thead>
<tr>
<th>Antibody/Drug-Conjugate</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trastuzumab</strong></td>
<td>1b A</td>
</tr>
<tr>
<td>- Cardiotoxicity in the adjuvant setting (0.8–4.0%)</td>
<td>1b A</td>
</tr>
<tr>
<td>- Troponin I might identify patients who are at risk for cardiotoxicity</td>
<td>2b B</td>
</tr>
<tr>
<td><strong>Bevacizumab</strong></td>
<td>1a A</td>
</tr>
<tr>
<td>- Hypertonus, proteinuria, bleeding, left ventricular dysfunction,</td>
<td>1a A</td>
</tr>
<tr>
<td><strong>Pertuzumab</strong></td>
<td>2b B</td>
</tr>
<tr>
<td>- Skin rash, diarrhea, mucositis</td>
<td>2b B</td>
</tr>
<tr>
<td><strong>T-DM1</strong></td>
<td>2b B</td>
</tr>
<tr>
<td>- Thrombocytopenia, hepatotoxicity pyrexia, headache, pneumonitis</td>
<td>2b B</td>
</tr>
</tbody>
</table>
Small Molecules

Lapatinib
- Diarrhea, skin rash, fatigue

Everolimus
- Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, thrombocytopenia

PARP-inhibitors (olaparib)
- Fatigue, myelosuppression

CDK4/6 inhibitors (palbociclib, LEE011)
- Myelosuppression, neutropenia
Immun-Checkpoint Inhibitors

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
Pneumonitis-Management PD1/ PDL1-Inhibitors

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-limition, oxygen need) ➔ Discontinue ➔ i.v. 1-2 mg/kg BW methylprednisolone † ‡

IV° (life threatening, Indication for tracheotomy / intubation) ➔ Discontinue ➔ i.v. 1-2 mg/kg BW methylprednisolone, evtl. after 48-72h + Infliximab/ MMF/ Endoxane ‡

* Prophylactic antibiotics using ciprofloxacin 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 deesclalated over 1 month
‡ Any Pneumonitis > grade III bronchoscopy using BAL/ with sampling

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017
Nephritis-Management PD1/PDL1-Inhibitors

I° (Creatinine< 2 g/dL) ➔ Continue ➔ Follow up to exclude pre- and postrenal failure

II° (Creatinine< 3 g/dL) ➔ Discontinue ➔ Oral 0,5-1 mg/kg BW methylprednisolone* †

III° (Creatinine> 3 g/dL) ➔ Discontinue ➔ I.v. 1-2 mg/ kg BW methylprednisolone † ‡

IV° Requiring dialysis: (hypervolemia / hyperkalemia / azotemia/ pericardal rubbing) ➔ Discontinue ➔ Continue as instructed by the nephrologist

* * Prophylactic antibiotics using ciprofloxacin 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
Hypophysitis-Management PD1/ PDL1-Inhibitors

TSH/fT3/ fT4 suppressed +/- Hyperkalemia +/- Hypoglycemia +/- Hypotonus +/- Fatigue -> suspicion of Autoimmune- Hypophysitis/ central Addison

ACTH †, Cortisol-Serum, 24h-urine for Cortisol, PRL †, IGF-1 †, FSH/ LH (Premenopause), ECG, Vital signs followed by Hypophysal- MRI ‡

Methylprednisolone 1-2 mg/ kg BW i.v.*!
Further Hormonal substitution (L-Thyroxin) after counselling Endocrinologist

† ACTH: adrenocorticotropic hormone, PRL: Prolactin, IGF-1: insulin growth factor-1
‡ Hypophysial-MRI after counselling neuroradiologist
* Stop treatment with Checkpoint-Inhibitors, prophylactic antibiotics with Ciprofloxacin 500 mg bid p.o., gastric ulcer prophylaxis with PPI, oral Potassium substitution.
Deescale Methylprednisolone (reduced bioavailability 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
# Hepatitis-Management PD1/ PDL1-Inhibitors

<table>
<thead>
<tr>
<th>Stage</th>
<th>ALAT/ ASAT</th>
<th>Total-Bili</th>
<th>Action</th>
<th>Further Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I°</td>
<td>(ALAT/ ASAT &lt; 3 x ULN and/or Total-Bili &lt; 1,5 x ULN)</td>
<td></td>
<td>Continue</td>
<td>LFT-control before next treatment</td>
</tr>
<tr>
<td>II°</td>
<td>(ALAT/ ASAT &lt; 5 x ULN and/or Total-Bili &lt; 3 x ULN)</td>
<td></td>
<td>Discontinue</td>
<td>&gt; 5-days persistence: 1 mg/kg BW po methylprednisolone* †</td>
</tr>
<tr>
<td>III°</td>
<td>(ALAT/ ASAT &gt; 5 x ULN and/or Total-Bili &gt; 3 x ULN)</td>
<td></td>
<td>Discontinue</td>
<td>2 mg/kg BW i.v. methylprednisolone †</td>
</tr>
<tr>
<td>IV°</td>
<td>(ALAT/ ASAT &gt; 20 x ULN and/or Total-Bili &gt; 10 x ULN)</td>
<td></td>
<td>Stop</td>
<td>2 mg/kg BW i.v. methylprednisolone, evtl after 48h + MMF 1000 mg bid</td>
</tr>
</tbody>
</table>

* 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 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)
**Colitis-Management PD1/ PDL1-Inhibitors**

- **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*
Thyroiditis-management PD1/PDL1-inhibitors

TSH reduced, fT3/ fT4 elevated – suspecting autoimmune thyroiditis

Thyreoglobulin, MAKs †, TAKs †, TRAKs †, ECG, vital signs, followed by thyroid gland-sono. Th Lumps/ Hyperemia ‡

Management according to the guidelines of the endocrinologists:
carbimazole 10 mg/d ! according to symptoms increase carbimazole to 20 mg/d +/- Propranolol 5 mg bid +/- methylprednisolone 1-2 mg/kg BW i.v.*
In difficult to manage admission as inpatient for thiamizole i.v.

† MAKs: anti-TPO antibodies, TAKs: anti-thyroglobulin-antibodies, TRAKs: anti-TSH-receptor-antibodies
‡ Thyroid gland sonography in endocrinology-outpatient clinic, refer
! With carbimazole 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 ciprofloxacin 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 bioavailability of oral steroids

Courtesy, A.Schneeweiss, NCT, UFK Heidelberg, 2017
Häufigste Nebenwirkungen im Verlauf einer Langzeit-Therapie mit Palbociclib in PALOMA-1

<table>
<thead>
<tr>
<th>Therapiedauer</th>
<th>0 ≤ 6 Monate (n = 95)</th>
<th>6 ≤ 12 Monate (n = 77)</th>
<th>12 ≤ 18 Monate (n = 59)</th>
<th>18 ≤ 24 Monate (n = 40)</th>
<th>≥ 25 Monate (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jegliche UE</td>
<td>97,9</td>
<td>88,3</td>
<td>81,4</td>
<td>72,5</td>
<td>79,3</td>
</tr>
<tr>
<td>Neutropenie</td>
<td>69,5</td>
<td>54,5</td>
<td>44,1</td>
<td>40,0</td>
<td>51,7</td>
</tr>
<tr>
<td>Leukopenie</td>
<td>33,7</td>
<td>27,3</td>
<td>16,9</td>
<td>20,0</td>
<td>13,8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33,7</td>
<td>14,3</td>
<td>13,6</td>
<td>10,0</td>
<td>10,3</td>
</tr>
<tr>
<td>Übelkeit</td>
<td>23,2</td>
<td>6,5</td>
<td>5,1</td>
<td>2,5</td>
<td>6,9</td>
</tr>
<tr>
<td>Anämie</td>
<td>22,1</td>
<td>19,5</td>
<td>15,3</td>
<td>15,0</td>
<td>13,8</td>
</tr>
<tr>
<td>Diarrhoe</td>
<td>18,9</td>
<td>0</td>
<td>5,1</td>
<td>2,5</td>
<td>10,3</td>
</tr>
<tr>
<td>Alopezie</td>
<td>16,8</td>
<td>2,6</td>
<td>1,7</td>
<td>0</td>
<td>3,4</td>
</tr>
<tr>
<td>Hitzewallung</td>
<td>16,8</td>
<td>7,8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gelenkschmerzen</td>
<td>12,6</td>
<td>10,4</td>
<td>15,3</td>
<td>7,5</td>
<td>13,8</td>
</tr>
<tr>
<td>Dyspnöe</td>
<td>12,6</td>
<td>2,6</td>
<td>6,8</td>
<td>0</td>
<td>3,4</td>
</tr>
<tr>
<td>Appetitminderung</td>
<td>10,5</td>
<td>7,8</td>
<td>0</td>
<td>2,5</td>
<td>0</td>
</tr>
</tbody>
</table>

UE: unerwünschtes Ereignis
**Monitoring Palbociclib**

## 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

<table>
<thead>
<tr>
<th>CTCAE-Grad (Neutrophilenzahl)</th>
<th>Dosisanpassungen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grad 1 (&lt; unterer Grenzwert bis 1500/ml)</td>
<td>keine Dosisanpassung erforderlich</td>
</tr>
</tbody>
</table>
| Grad 2 (1000 bis ≤ 1500/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: 

| Grad 3\(^a\) (500 bis < 1000/μl) | **Therapiepause** bis ≥ 1000/μl Neutrophilie. Wiederaufnahme mit 1 Dosisstufe niedriger. |
| Grad 3 (500 bis < 1000/μl) + Fieber ≥ 38,5 °C und/oder Infektion | **Therapiepause** bis ≥ 1000/μl Neutrophilie. Wiederaufnahme in der nächst niedrigeren Dosisstufe. |
| Grad 4\(^a\) (< 500/μl) | **Therapiepause** bis ≥ 1000/μl Neutrophilie. Wiederaufnahme in der nächst niedrigeren Dosisstufe. |

---

N. Harbeck, J.Ettl, Drug Report, 2017
## Adverse Effects of Olaparib

<table>
<thead>
<tr>
<th>Adverse effects (AE):</th>
<th>Grade and occurrence</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal AE</strong></td>
<td>- mostly gr. 1-2,</td>
<td>- interruption /</td>
</tr>
<tr>
<td>(Nausea, vomiting, diarrhea):</td>
<td>- no prophylactic antiemetics necessary</td>
<td>- dose reduction</td>
</tr>
<tr>
<td></td>
<td>- interruption / /</td>
<td>- antiemetics</td>
</tr>
<tr>
<td></td>
<td>- no prophylactic antiemetics necessary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- CBC at the start and monthly (in the first 12 months</td>
<td></td>
</tr>
<tr>
<td><strong>Hematological AE</strong></td>
<td>- mostly gr. 1-2,</td>
<td>- interruption /</td>
</tr>
<tr>
<td>(anemia, leucopenia, thrombocytopenia):</td>
<td>- CBC at the start and monthly (in the first 12 months</td>
<td>- dose reduction</td>
</tr>
<tr>
<td></td>
<td>- interruption / /</td>
<td>- if nec. GCSF, transfusion</td>
</tr>
<tr>
<td><strong>Neurological system</strong></td>
<td>- mostly gr. 1-2,</td>
<td>- interruption /</td>
</tr>
<tr>
<td>(headache, dizziness):</td>
<td>- interruption / /</td>
<td>- dose reduction</td>
</tr>
<tr>
<td><strong>Metabolism / Diet</strong></td>
<td>- mostly gr. 1-2,</td>
<td>- interruption /</td>
</tr>
<tr>
<td>(reduced appetite):</td>
<td>- interruption / /</td>
<td>- dose reduction</td>
</tr>
<tr>
<td></td>
<td>- interruption / /</td>
<td></td>
</tr>
</tbody>
</table>
Therapy Side Effects (2/35)

Further information:

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
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.

Acute Toxicity according to WHO\(^1\) or NCI-CTC\(^2\):

**References:**

2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010);
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

References:


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

No further information

References:

See slide 5
Peripheral Neuropathy (7/35)

No further information

References

3. S3-Leitlinie Supportive Therapie bei onkologischen PatientInnen Langversion 1.0 – November 2016 AWMF-Registernummer: 032/0540L
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 asymptomatic cardiac disease defined as the decline in left ventricular ejection fraction of more than 10 % to an ejection fraction of less than 55 %. Similar data were presented recently by Perez et al. in N9831 trial. In 2992 patients completed AC 5% had LVEF decrease disallowing trastuzumab (decrease below normal: 2.4%, decrease > 15%: 2.6%).

FAC: The Southwest Oncology Group evaluated long term 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 comorbidities and a higher risk of recurrence. The hazard ratios for cardiomyopathy, cardiac failure, and heart disease for patients > 65 years treated with doxorubicin compared with patients who received no chemotherapy were 2.48 (95% CI, 2.10 to 2.93), 1.38 (95% CI, 1.25 to 1.52), and 1.35 (95% CI, 1.26 to 1.44), respectively. The relative risk remained elevated 5 years after diagnosis. Preexisting heart disease was beside of afro-american race the most important risk factor for cardiac failure after A-exposure.

Pinder et al reported data from a total of 43,338 women from the SEER’S database. Similarly as in the previous study anthracycline–treated women were younger, with less comorbidity and had more advanced diseases than women who received non anthracycline based regimens. The adjusted hazard ratio was 1.26 for women aged 66 to 70 treated with a compared other chemotherapy. In this age group at five years of follow-up the observed absolute differences were of 1% and 4.6% respectively in rates of chronic heart failure between anthracycline based chemotherapy and other adjuvant chemotherapy or no chemotherapy. After ten years the increased risk of chronic heart failure was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when comparing anthracycline treated patients to the other or no adjuvant chemotherapy groups. For women aged 71 to 80 adjuvant chemotherapy was not associated with chronic heart failure.

Taxanes and cardiac safety

Data on cardiac safety in anthracycline-taxane sequential trials are in favour of taxane-based combinations, in which lower doses of anthracyclines are used. E.g. the PACS 01 trial reported significantly lower incidence of cardiac toxicity in the 3xFEC-3xDoc arm than in the 6xFEC arm (0.4% vs. 1.3%, p=0.027). These data have been confirmed in the Cochrane analysis, where trials in which total doses of anthracycline was reduced by substitution of taxane, had subsequently less
cardiac events, than standard A-based regimens (OR=0.37 (95%CI: 0.14-0.95)). There are only limited data on cardiac safety of A-free regimens in adjuvant setting in breast cancer. Jones et al. reported 5 cardiac events in 510 patients treated by 4 cycles of AC and only 1 in 506 patients in the 4xTC arm in the US Oncology study.

In the BCIRG 006 study there were also significantly less patients with >10% decrease of LVEF value in the Taxotere/Carboplatin/Herceptin (TCH) arm than in AC-TH arm (8% vs. 17,3%), although the negative synergistic cardiac effect of Herceptin should be considered separately of anthracycline cardiac side effects.

Trastuzumab and cardiac safety

Most studies have excluded elderly patients (> 60 or 65 years) or patients with other risk factors (cardiovascular diseases, obesity, hypertension) from studies including trastuzumab. In clinical practice, 32% of HER2+ EBC patients treated with trastuzumab are 'over-60'. These patients have an increased cardiovascular risk profile and develop trastuzumab related cardiotoxicity commonly. Also with regard to other risk factors there is an increased risk of trastuzumab related cardiotoxicity during treatment, which is reversible after cessation of trastuzumab.

References:

Statements

“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m²
cum. dose, resp.)”

“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”


“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently…”


“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”


“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”

Further references:


Further information:

The frequency of adverse events for patients with HER-2 positive early breast cancer was examined in a randomized study with a median follow-up time of 3.7 years. 1503 patients were irradiated. Radiotherapy (RT) was administered either without or with concurrent trastuzumab (H). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of cardiac events (CEs) regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% v 5.9% with or without RT, respectively. Thus, concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (Halyard al, 2009). Reported data regarding the influence of tamoxifen given simultaneously to radiotherapy are diverging. Simultaneously given tamoxifen to radiotherapy might increase the risk of Grade 1 lung fibrosis (p = 0.01) and might increase the risk of late lung sequelae (OR = 2.442, 95% CI 1.120-5.326, p = 0.025). However other reports did not confirm such an connection. Therefore the results of the ongoing CONSeT-trials has to be awaited.

References:

Statements
“Trastuzumab simultaneous to radiotherapy”

“Trastuzumab simultaneous to epirubicin”


“Trastuzumab simultaneous to doxorubicin”


“Anthracycline simultaneous to radiotherapy”

“Tamoxifen simultaneous to radiotherapy”


Further references:


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 trastuzumab and placebo or to docetaxel and trastuzumab and pertuzumab. LVEF dysfunction (any grade) was more frequently seen in the placebo group than in the pertuzumab group (8.3% vs 4.4%). LVEF dysfunction of grade 3 or higher was reported in 2.8% and 1.2% of the patients in the placebo and pertuzumab arms respectively.

**References:**


Secondary Malignancies I (12/35)

Further information:

Approximately one in every 20 breast cancer patients developed a second non-breast primary tumour within 10 years following a breast cancer diagnosis (10 years cumulative incidence rate 5.4%; 95%CI 5.1 to 5.7). Compared with the general female Dutch population, these breast cancer patients had a 22% increased relative risk in second non-breast primary cancers and an absolute excess risk of 13 cases per 10,000 women-years (13.6 (95%CI 9.7 to 17.6). The occurrence of a second non-breast cancer was associated with a decrease in overall survival (HR 3.98, 95%CI 3.77 to 4.20). 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.

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. Patients 50 years and older, radiotherapy was associated with increased risk of soft tissue sarcoma (HR 3.43, 95%CI 1.46 to 8.04), chemotherapy with increased risk of melanoma, uterine cancer, acute myeloid leukemia and hormonal therapy with uterine cancer (HR 1.78, 95%CI 1.40 to 2.27).

Risk of secondary acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

Women with a prior breast cancer were ~2.6 times more likely to develop AML than the total female Australian population, with highest age-specific relative risk for AML in the 30- to 49-age group. Mitoxaontrone-based chemotherapy was associated with a higher leukemic risk than with anthracyclines (RR 16.8, 95%CI 7.1 to 34.2 than RR 2.7, 95%CI 1.7 to 4.5). Epirubicin and doxorubicin had a similar risk. For women > 65 years receiving polychemotherapy (CAF, ACP) the risk to develop grade 4 hematologic toxicity, to have discontinued treatment for toxicity or to die of acute myeloid leukemia/MDS was significantly elevated. Granulocyte colony-stimulating factor (G-CSF) increased the risk of developing AML/MDS.
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.
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).

References for statements 1-4:


Reference for Statement Tamoxifen and endometrial cancer


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 (0.5-0.9 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 consistent 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.\(^6\)\(^-\)\(^8\)

References:


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. After modern taxanthracyclin 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%. 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 disesease-free and overall survival regardless of treatment, in particular when the tumor was ER-positive. The dose of drug delivered was not a key factor explaining the differences.

References:
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.
References:

Fatigue is frequently present...


**Psycho-social interventions...**

Physical exercise.....


Methylphenidate...

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).

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).
References:

Sleep disturbances are a common problem....


Behavioral therapies have demonstrated efficacy.....

(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.

References:

Statements 1-4


Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al., 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al., 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al., 2005). Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al., 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al., 2010).

The biologic base for these changes is unclear. However, there are several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms (Ahles et al., 2007).

Cognitive behavioral therapy might lead to significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups (Ferguson et al., 2007). Other potential treatment approaches include methylphenidate, which has been used to improve cognitive
function in patients with advanced cancer. E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R130#R130

E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R110#R110

References:

Therapy-related cognitive deficits (chemobrain)...


Cognitive-behavioral therapy....
Methylphenidate might improve cognitive function....

**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 occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

*References:*

Side-Effects and Toxicity – of Bone Modifying 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).

References:


Acute phase rea
Gastrointestinal side effects...

**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.

*References:*

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 tyrosinkinase-inhibitor lapatinib which led to the approval of lapatinib in advanced HER-2 positive breast cancer, asymptomatic cardiac events were identified in four women in the combination-therapy group and in one woman in the monotherapy group. All of these events in the combination-therapy group were considered to be related to treatment, and all women had an LVEF value that was at or above the lower limit of the normal range on subsequent assessment.
The most common adverse events were diarrhea, the hand–foot syndrome, nausea, vomiting, fatigue, and rash that was distinct from the hand–foot syndrome. Most adverse events were grade 1, 2, or 3. Grade 4 diarrhea occurred in two women in the combination-therapy group (1%). One case each of grade 4 fatigue, headache, and dizziness was reported in the monotherapy group. Diarrhea, dyspepsia, and rash occurred more often in the group of women who received combination therapy.

A systematic review and meta-analysis of five randomized phase III clinical trials that used bevacizumab alone or in combination with chemotherapy in metastatic breast cancer showed a statistically significant bevacizumab associated increased risk for proteinuria (OR=27.68), hypertension (OR=12.76), left ventricular dysfunction (OR=2.25) and hemorrhagic events (OR=4.07), while no increased incidence was found for gastrointestinal perforation, vascular or fatal events and febrile neutropenia, respectively.

References

Cardiotoxicity....


**Troponin I...**


**Bevacizumab ....**


**Lapatinib...**


**Pertuzumab**


**T-DM1**


**Everolimus:**

Immun-Checkpoint Inhibitors (25-26/35)

No further information

References:

**Palbociclib**

**Ribociclib**

**Everolimus**

Olaparib


Neratinib

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

No further information

No references
No further information

No references
No further information

No references
Hepatitis-Management PD1/PDL1-Inhibitors (30/35)

No further information

No references
No further information

No references
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
Supportive Care
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
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)

- Indicated in asymptomatic anaemia

- Therapy and secondary prophylaxis in CIA
  - In the adjuvant setting
  - In the neoadjuvant/metastatic setting

- In dose-dense / dose-escalated CT (iddETC)
- Treatment start at Hb-levels < 10 g/dL
- Target Hb 11–12 g/dL
- Improvement of outcome (DFS, OS)
- Risk of thromboembolic events is increased by use of ESAs

<table>
<thead>
<tr>
<th>Oxford / LoE / AGO</th>
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<td>1a</td>
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</tbody>
</table>

www.ago-online.de
# Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemia Patients with Metastatic Breast Cancer

N=2,098 Pat., Hb <11g/dl; non inferiority study.  
Prespecified upper non inferiority margin = 1.15

<table>
<thead>
<tr>
<th></th>
<th>PFS (median)</th>
<th>OS (median)</th>
<th>ORR</th>
<th>RBC transfusions</th>
<th>TVE</th>
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<tbody>
<tr>
<td><strong>Epo</strong></td>
<td>Invest.* 7,4 Mon</td>
<td>IRC** 7,6 Mon</td>
<td>17,2 Mon</td>
<td>50%</td>
<td>5,8%</td>
</tr>
<tr>
<td><strong>BSC</strong></td>
<td>7,4 Mon.</td>
<td>7,6 Mon.</td>
<td>17,4 Mon</td>
<td>51%</td>
<td>11,4%</td>
</tr>
</tbody>
</table>

- **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
Practical Use of ESAs

- 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 β: 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
Relevant Guidelines

Granulocyte Colony-stimulating Factors

- **Primary prophylaxis for expected febrile neutropenia (FNP)**
  - If expected risk for FNP 10–20%
    - In case of individual risk factors
  - If expected risk for FNP >20% (e.g. DAC, dose-dense CT)

- **Secondary prophylaxis during chemotherapy**
  (previous FNP or neutropenia grade IV > 7 days)

- **Therapeutic usage for FNP**

- **Start related to chemotherapy and duration**
  - Pegfilgrastim day 2
  - Lipegfilgrastim day 2
  - Filgrastim/Lenograstim from day 2–3 until ANC > 2–3 x 10⁹

<table>
<thead>
<tr>
<th>Oxford / LoE / GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prophylaxis for expected febrile neutropenia (FNP)</td>
<td>1b</td>
</tr>
<tr>
<td>If expected risk for FNP 10–20%</td>
<td>3b</td>
</tr>
<tr>
<td>In case of individual risk factors</td>
<td>1a</td>
</tr>
<tr>
<td>If expected risk for FNP &gt;20% (e.g. DAC, dose-dense CT)</td>
<td>1b</td>
</tr>
<tr>
<td>Secondary prophylaxis during chemotherapy (previous FNP or neutropenia grade IV &gt; 7 days)</td>
<td>1b</td>
</tr>
<tr>
<td>Therapeutic usage for FNP</td>
<td>1a</td>
</tr>
<tr>
<td>Start related to chemotherapy and duration</td>
<td>Pegfilgrastim day 2</td>
</tr>
<tr>
<td>Lipegfilgrastim day 2</td>
<td>1b</td>
</tr>
<tr>
<td>Filgrastim/Lenograstim from day 2–3 until ANC &gt; 2–3 x 10⁹</td>
<td>1b</td>
</tr>
</tbody>
</table>
Management of Febrile Neutropenia


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)

<table>
<thead>
<tr>
<th>Action</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Daily evaluation</td>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Hospitalization of high risk patients</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Homecare in low risk patients</td>
<td>1b</td>
<td>A</td>
<td>+</td>
<td></td>
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<tr>
<td>Differential blood count</td>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
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<tr>
<td>Blood cultures</td>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Imaging of lungs</td>
<td>3</td>
<td>C</td>
<td>++</td>
<td></td>
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<tr>
<td>Immediate initial empiric antibiotic therapy</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Empiric antifungal therapy 4–7d in case of failure of antibiotic therapy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>G-CSF for treatment (not prophylactic)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>
Empirical Antibiotic Therapy

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

- FN risk ≤10%
- FN risk 10-20%
- FN risk ≥20%

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

**High risk:**
- Age >65 years

**Increased risk:**
- Advanced disease
- History of prior FN
- No antibiotic prophylaxis

**Other Factors:**
- Poor performance (ECOG > 1)
- Female gender
- Haemoglobin <12 g/dL
- Liver, renal or cardiovascular disease
- Nutritional status

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

- Overall FN risk ≥20%
- Overall FN risk <20%

**Prophylactic G-CSF recommended**

**G-CSF prophylaxis not indicated**

Reassess at each cycle
Relevant Guidelines

Prophylaxis of Infections
rarely applicable to Patients with Solid Tumors (e.g. BC)
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

- Avoidance of highly infection-risking behaviour or situations
- Prophylactic treatment in low risk patients
- Prophylactic treatment in high risk* patients (e.g. according to NCCN Guidelines) with
  - Antibiotics
  - Anti-fungal agents (triazole)
  - Virostatics in solid tumors
  - Granulocyte colony-stimulating factors

* High risk: estimated duration of neutropenia < 100/µl > 7d
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.

This entails:

1) Patient:
   - Regular mouth washes (H₂O, NaCl)
   - Soft tooth brushes
   - Interdental care: flossing or using interdental brush
   - Avoidance of alcohol, tabac, hot food, sour food
   - Regular screening for lesions

2) Risk adjusted prophylaxis by dentist

3) Continuous clinical control
Mucositis


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

- Dexrazoxane for treatment of Anthracyclin-Paravasates (exception: liposomal A)
  - Oxford / AGO LoE / GR
    - 2b B ++

- Hyaluronic Acid for treatment of Taxan/Vinorelbin-Paravasates
  - Oxford / AGO LoE / GR
    - 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
### Antiemetic Therapy

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>LoE</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>After assessment of emetic potential of chemotherapy protocol</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Neurokinin-1-receptor-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Fixed antiemetic combination therapy</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>3b</td>
<td>C</td>
<td>+</td>
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</table>
Supportive Therapy
Antiemetics


## Supportive Therapy
### Antiemetics

<table>
<thead>
<tr>
<th>Substance group</th>
<th>Substance</th>
<th>Dosage</th>
<th>Side effects</th>
<th>Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serotoninantagonists</strong></td>
<td>Ondansetron</td>
<td>8 mg i.v., 2 x 4-8 mg p.o, transdermal</td>
<td>Headaches, Diarrhea, flush symptoms, increase of transaminases, intestinal atony at high dosages.</td>
<td>Very high</td>
</tr>
<tr>
<td></td>
<td>Tropisetron</td>
<td>5 mg i.v., 5 mg p.o.</td>
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<tr>
<td></td>
<td>Granisetron</td>
<td>1-3 mg i.v.</td>
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<tr>
<td></td>
<td>Palonosetron</td>
<td>0, 25 mg i.v.</td>
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</tr>
<tr>
<td><strong>NK1-Antagonists</strong></td>
<td>Aprepitant</td>
<td>125 mg d1, 80 mg d 2-3 p.o.</td>
<td>Cytochrom-P-450-activation with dose reduction of Dexamethasone (2 x 8 mg). Do not combine with Astemizol, Terfenadin, Cisaprid</td>
<td>Very high</td>
</tr>
<tr>
<td></td>
<td>Fosaprepitant</td>
<td>150 mg d1 i.v.</td>
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</tr>
<tr>
<td><strong>Dopaminantagonists/substituted Benzamids</strong></td>
<td>Metoclopramid</td>
<td>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.)</td>
<td>Dyskinesia (Antidot:Biperiden) Anxiousness, Depression, Diarrhea</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Alizaprid</td>
<td>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.)</td>
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<tr>
<td><strong>Phenothiazins/Butyrophenons</strong></td>
<td>Haloperidol</td>
<td>1-3 mg 4 x/d</td>
<td>Sedation, Cramps, transient increase of biochemical liver function values</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Dexamethason</td>
<td>8-20 mg i.v. 1-3 x/d</td>
<td>Extreme blood sugar values, psychotic reactions, flush syndrome, Hypertension</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Prednisolon</td>
<td>100-250 mg i.v. 1-3 x/d</td>
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</tr>
<tr>
<td><strong>NEPA (Netupitant and Palonosetron)</strong></td>
<td>fixed combinations (oral)</td>
<td>NE 300 mg PA 0,5 mg</td>
<td></td>
<td>Very high</td>
</tr>
</tbody>
</table>
Analgesia
(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie Tumorschmerz 2014 www.dgs-praxisleitlinien.de)

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofene and / or metamizole, paracetamole

- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations)
  or tilidine / naloxone (also as „retard“-formulations)

- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl
  (transdermal), hydromorphone, oxycodone, as 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
Diarrhea

- Adsorbent agents
  - Carbo medicinalis; caoline / pectine, Al-Mg-silicate hydrate

- Analgetics, opioids
  - Loperamide; codeine, morphine IV, tinctura opii, butylscopolamine

- Colitis pseudomembranosa
  - Metronidazols or (if not effective) vancomycine
Constipation
Important Side Effect of Opioid Treatment

- **Bulging agents**
  - Psyllium, flaxseed (shredded)

- **Osmotic laxatives**
  - Macrogol > Lactulose (Cochrane review LoE 1a, AGO +)
  - Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate
  - Sorbite

- **Motility stimulating laxatives**
  - Sennae, Ricinus, Bisacodyl, sodium-picosulfate

- **Emollients** (Internal lubricants e.g. paraffin)

- **Opioid-receptor-antagonists (in opioid-related constipation)**
  - MethylNaltrexone
Avoidance of chemotherapy-induced alopecia
by cooling the patient’s scalp*

Prophylaxis of hand-foot-syndrome
using urea containing lotions (5-10%)

Prophylaxis of nail changes and hand-foot-syndrome by cooling hands during application of docetaxel

*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

Design
Randomized trial, scalp cooling device vs. control

Assessed for: alopecia, quality of life, device safety

Results
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
Physical activity reduces the functional losses

There is no effective prevention of CIPN

- Alpha-liponic acid
- Amifostine
- Carbamazepine
- Vit E
- L-Carnitine

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
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

- Physical Therapy
- Duloxetine for pain induced by CIPN
- Gabapentine
- Amitryptiline
- Venlafaxine
- Pregabaline
- Lamotrigine
- Opioids for treatment of CIPN-induced pain
- Capsaicine / Lidocaine locally
- Menthol locally (1%)
- Baclofene

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>AGO GR</th>
</tr>
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<tbody>
<tr>
<td>Physical Therapy</td>
<td>5</td>
<td>+</td>
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</tr>
<tr>
<td>Duloxetine for pain induced by CIPN</td>
<td>1b</td>
<td>+</td>
<td></td>
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<tr>
<td>Gabapentine</td>
<td>1b</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>1b</td>
<td>+</td>
<td></td>
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<tr>
<td>Venlafaxine</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pregabaline</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1b</td>
<td>-</td>
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</tr>
<tr>
<td>Opioids for treatment of CIPN-induced pain</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Capsaicine / Lidocaine locally</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Menthol locally (1%)</td>
<td>5</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Baclofene</td>
<td></td>
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</tr>
</tbody>
</table>
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.”

➢ “Palliative care should be initiated by the primary oncology team and augmented by collaboration with an interdisciplinary team of palliative care experts.”

➢ “Expert palliative care, including effective control of pain and other symptoms, should be a priority.”

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


Phase III Study of Epoetin Alfa Versues Best Standard of Care ...(5/28)

No further information

References:

Practical use of ESAs (6/28)

No further information

References:


Relevant Guidelines

Relevant Guidelines (7/28)

No further information

No references
Granulocyte Colony-stimulating Factors (8/28)

No further information

References:

**Management of Febrile Neutropenia (9/28)**

*No further information*

**References:**

Empirical Antibiotic Therapy (10/28)

No further information

No references
EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment (11/28)

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

References:


Relevant practice guideline:

Paravasation Dexrazoxane/Hyaluronic Acid (17/28)

No further information

No references
Antiemetic Therapy (18/28)

No further information

References:


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

References:

1. 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
Prevention of CIPN, (chemotherapy induced peripheral polyneuropathia) (26/28)

No further information

References:


Relevant practice guideline:

Therapy of CIPN (27/28)

No further information

References:

1. www.mascc.org
2. Keith B.: Systematic review of the clinical effect of glycocorticoids on nonhematologic malignancy BMC Cancer (2008);8:84
7. Massa E, Astara G, Madeddu C, Dessì M, Loi C, Lepori S, Mantovani G. Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response. Crit Rev Oncol Hematol. 2008 Aug 23. [Epub ahead of print]


Relevant practice guideline:

Palliative Care (28/28)

No further information

No references
Breast Cancer: Specific Situations
Breast Cancer: Specific Situations

- **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
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)
Breast Cancer in Young Women ≤ 35 Years

- Aggressive biological behavior with worse prognosis
  - LoE: 2a, GRADE: B

- Surgery like patients ≥ 35 y
  - LoE: 2b, GRADE: B +

- Guidelines adapted (neo-)adjuvant systemic treatment (see chapters there)
  - LoE: 1b, GRADE: A ++

- GnRHa as ovarian protection (see chapter gyn. problems)
  - LoE: 1b, GRADE: B +

- Genetic and fertility counseling
  - LoE: 2b, GRADE: B ++

- Contraception counseling
  - LoE: 2b, GRADE: B ++
Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery

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

* Participation in register study recommended
Breast Cancer During Pregnancy - (Neo-)adjuvant Therapy -

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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE</th>
<th>GR</th>
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<tr>
<td>Bisphosphonates, denosumab</td>
<td>4</td>
<td>D</td>
<td>-</td>
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</tbody>
</table>
Breast Cancer During Pregnancy*  
- Delivery and Breast-Feeding-

- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)
- Termination of pregnancy does not improve maternal outcome
- Delivery mode like in healthy women, avoid delivery ≤3 weeks from last cycle of chemotherapy
- If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities

* Participation in register study recommended
After breast cancer diagnosis reproductive techniques can be used to induce pregnancy

Success rates for getting pregnant and for delivering a child are lower in breast cancer patients in comparison to non-cancer patients

Breast cancer patients of reproductive age should be offered a fertility counseling before starting any kind of treatment

Breast cancer patients should not be advised against getting pregnant regardless of tumor’s hormone receptor status
Pregnancy Associated Breast Cancer*: Outcome

- BC during pregnancy / lactation
  - Adequate treatment is essential

- Pregnancy and lactation after BC
  - Outcome not compromised

* Participation in register study recommended

Oxford LoE
3a
Geriatric Assessment

- No specific algorithm is available
- Ability to tolerate treatment varies greatly („functional reserve“)
- Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services

Assessment tools:
- Charlson Comorbidity Index (widely used; good predictor over a 10-year period)
- 12 prognostic indicators to estimate 4-year mortality risk
- Short screening tests (more qualitative evaluation)
- IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8
- Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)
Treatment for Fit Elderly Patients
(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

- Clinical geriatric assessment
- Treatment according to guidelines
  - Surgery similar to „younger“ age
  - Endocrine treatment (endocrine resp.)
  - Chemotherapy (standard regimens)
    - < 70 years
    - > 70 years (especially N+, ER/PgR-)
- Radiotherapy
- Omit radiotherapy after BCT in low risk with endocrine treatment
- Trastuzumab

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>B</th>
<th>++</th>
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<tbody>
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<td>C</td>
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<td>2b</td>
<td>2b</td>
<td>B</td>
<td>++</td>
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<td>1a</td>
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<td>+</td>
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<tr>
<td>2a</td>
<td>2a</td>
<td>C</td>
<td>+*</td>
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<tr>
<td>1a</td>
<td>1a</td>
<td>A</td>
<td>+</td>
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<td>1b</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2b</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

*Study participation recommended
Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

- Reduced standard treatment
  
- Options extrapolated from trials in elderly:
  - No breast surgery
    (consider endocrine options)
  - No axillary clearing (≥ 60 y, cN0, rec.-pos)
  - No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)
  - Hypofractionated radiotherapy
  - No chemotherapy if >70 years and negative risk-benefit analysis

Oxford / AGO LoE / GR

2b C ++

2b C +

2b B +

1b B ++

2b B +

2b C +
Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

- **Diagnostic work-up as in women**
  - Mammography
  - Ultrasound
- **Standard-surgery: Mastectomy**
  - BCT is an option (tumor breast relation)
  - Sentinel-node excision (SNE)
- **Radiotherapy as in women**
  (consider tumor breast relation!)
- **Genetic counselling if one additional relative affected (breast/ovarian cancer)**
- **Screening for 2nd malignancies according to guidelines**

<table>
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<tr>
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<th>+</th>
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<td>B</td>
<td>++</td>
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<tr>
<td></td>
<td>GCP</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

*Participation in register study recommended*
Male Breast Cancer: Systemic Therapy

- **Adjuvant chemotherapy as in women**
  
- **HER2-targeted therapy**

- **Endocrine therapy**
  - Tamoxifen
  - Aromatase inhibitors (adjuvant)
  - Aromatase inhibitors (metastatic BC)
  - GnRHa and AI (metastatic BC)
  - Fulvestrant (metastatic BC)

- **Palliative chemotherapy as in women**

---

*Participation in register study recommended*
Benefit from Trimodal Treatment in Inflammatory Breast Cancer

<table>
<thead>
<tr>
<th>Median survival probability</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Trimodal therapy</td>
<td>1.00</td>
<td>-</td>
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<tr>
<td>Surgery alone</td>
<td>1.64</td>
<td>1.46 to 1.84</td>
</tr>
<tr>
<td>Surgery &amp; chemotherapy</td>
<td>1.47</td>
<td>0.96 to 2.24</td>
</tr>
<tr>
<td>Surgery &amp; radiotherapy</td>
<td>2.28</td>
<td>1.80 to 2.89</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall survival-probability (OS)</th>
<th>10 years-OS</th>
<th>5 years-OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimodal therapy</td>
<td>55.4%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Surgery &amp; chemotherapy</td>
<td>42.9%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Surgery &amp; radiotherapy</td>
<td>40.7%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>16.5%</td>
<td></td>
</tr>
</tbody>
</table>

Inflammatory Breast Cancer (IBC, cT4d)

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

Oxford / AGO LOE / GR

- ++
- 2c B ++
- 2c B +
- 2c B ++
- 2c B ++
- 2b C +/-
- 3b C -
- 2c B ++
Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary – Axillary CUP)

- **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**
### Imaging Diagnostics

- **Mammography, Breast-ultrasound, Breast-MRI**
  - Oxford / AGO LOE / GR: 3 B ++

- **Exclude contralateral cancer**
  - Oxford / AGO LOE / GR: 3 B ++

- **Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)**
  - Oxford / AGO LOE / GR: 5 D ++

- **Staging (CT thorax / abdomen, thyroid scintigraphy, HNT-exam)**
  - Oxford / AGO LOE / GR: 3 B ++

- **PET / PET-CT**
  - Oxford / AGO LOE / GR: 3b B +
Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Pathology, Molecular Pathology

- ER, PgR, HER2, GATA3

- Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.

- Gene expression profiling for determination or primary site (CUPprint, Pathwork, TOT, Theros CTID)

- NGS, epigenetics for determination of primary site (Panel-Sequencing, EPICup)

- Prognostic gene expression tests

<table>
<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
<th>5</th>
<th>D</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER, PgR, HER2, GATA3</td>
<td></td>
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<tr>
<td>Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.</td>
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<tr>
<td>Gene expression profiling for determination or primary site (CUPprint, Pathwork, TOT, Theros CTID)</td>
<td>2c</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>NGS, epigenetics for determination of primary site (Panel-Sequencing, EPICup)</td>
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<tr>
<td>Prognostic gene expression tests</td>
<td>5</td>
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Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Therapy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Grade</th>
<th>Evidence</th>
<th>Level</th>
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<tbody>
<tr>
<td>Axillary dissection</td>
<td>3a</td>
<td>C</td>
<td>++</td>
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<tr>
<td>Mastectomy if breast MRI is negative</td>
<td>3a</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>(Neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO)</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Breast irradiation if breast MRI is negative</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
</tr>
</thead>
</table>
| 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%) |
Paget’s Disease of the Breast Diagnosis

- Histological verification by skin biopsy ++
- Mammography, sonography 4 D ++
- MR of the breast if other imaging negative 4 C +
- Immunohistology (ER, PgR, HER2, Ck7) to detect benign and HER2-negative cases 5 D ++
# Paget’s Disease of the Breast

Therapy

- **Paget’s disease with underlying disease (invasive breast cancer, DCIS):**
  - Therapy according to standard of the underlying disease
  - Surgery must achieve R0

- **Isolated Paget’s disease of the NAC:**
  - Surgery must achieve R0
  - Surgical resection only, no adjuvant radiotherapy
  - Sentinel-node excision (SNE)

---

**Oxford / AGO LOE / GR**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LOE</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Paget’s disease with underlying disease</td>
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<td>Therapy according to standard of the underlying disease</td>
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<tr>
<td>Isolated Paget’s disease of the NAC</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Sentinel-node excision (SNE)</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Grading</td>
<td>Benign PT (75%)</td>
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<tr>
<td></td>
<td>Borderline PT (16%)</td>
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<tr>
<td></td>
<td>Malignant PT (9%)</td>
</tr>
<tr>
<td>Median age on diagnosis</td>
<td>Benign PT: 39 J.</td>
</tr>
<tr>
<td></td>
<td>Borderline PT: 45 J.</td>
</tr>
<tr>
<td></td>
<td>Malignant PT: 47 J.</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>Benign PT: 10 - 17%</td>
</tr>
<tr>
<td></td>
<td>Borderline PT: 14 - 25%</td>
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<tr>
<td></td>
<td>Malignant PT: 23 - 30%</td>
</tr>
</tbody>
</table>
Borderline and Malignant Phyllodes Tumor Diagnosis

- Mammography, sonography
- Diagnosis on core biopsy, grading on resection specimen
- Breast MRI
- Staging only malignant PT (CT thorax, skeletal system)

<table>
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<th>Evaluation</th>
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<tr>
<td>3</td>
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<tr>
<td>3</td>
<td>C ++</td>
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<tr>
<td>3</td>
<td>C +/-</td>
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<tr>
<td>5</td>
<td>D ++</td>
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</table>
Borderline and Malignant Phyllodes Tumor Surgery

- R0-Excision
- SNE / Axillary dissection when cN0
- Treatment of local recurrence
  - R0 resection or simple mastectomy

Oxford / AGO LOE / GR

- R0-Excision: 2b B ++
- SNE / Axillary dissection when cN0: 4 C -
- Treatment of local recurrence: 4 C ++
Borderline and Malignant Phyllodes Tumor

Adjuvant Therapy

- Adjuvant radiotherapy
  - If $T \geq 2 \text{ cm} (\text{BCT})$ or $T \geq 10 \text{ cm} (\text{mastectomy})$
  - Systemic adjuvant therapy (chemo, endocrine)
- Treatment of local recurrence
  - R0 resection or simple mastectomy
  - Radiotherapy, chemotherapy after R1 resection
- Distant metastases (very rare)
  - Treatment like soft tissue sarcomas

Oxford / AGO LOE / GR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Grade</th>
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<tr>
<td>Systemic adjuvant therapy (chemo, endocrine)</td>
<td>4 C -/</td>
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<td>R0 resection or simple mastectomy</td>
<td>4 C +/</td>
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<tr>
<td>Radiotherapy, chemotherapy after R1 resection</td>
<td>4 C ++</td>
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</tbody>
</table>
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

- Mammography, sonography to determine extent of disease
  - Oxford / AGO LOE / GR 3a C --

- Preoperative MRI to determine the extent of disease
  - Oxford / AGO LOE / GR 3a C ++

- Diagnosis by core biopsy
  - Oxford / AGO LOE / GR 3a C ++

- Diagnosis by FNB
  - Oxford / AGO LOE / GR 3a C --

- Staging (CT thorax & abd.; angiosarcoma: MRI brain)
  - Oxford / AGO LOE / GR 4 D ++

- Prognostic factors: size, grade, margins
  - Oxford / AGO LOE / GR 3a C ++

*Therapy in specialized centres recommended
Primary Angiosarcoma of the Breast*
Therapy

- Surgery with wide clear margins, mostly as mastectomy
  - Breast-conserving therapy
- SNB or axillary dissection if cN0
- Adjuvant chemotherapy (anthracycline/taxane-based)
- Adjuvant radiotherapy if high risk (size > 5 cm, R1)

Oxford / AGO
LOE / GR

<table>
<thead>
<tr>
<th>LOE</th>
<th>Grade</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
<td>- -</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* 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%
Secondary Angiosarcoma of the Breast Therapy

- Secondary mastectomy
- Adjuvant chemotherapy (anthracycline/taxane-based)
- Adjuvant radiotherapy if high risk (size > 5 cm, R1)
- Regional hyperthermia (to improve local control) plus chemotherapy and/or radiotherapy

Oxford / AGO LOE / GR

3a C ++
2b B +/-
2b B +/-
2b B +/-
## Angiosarcoma of the Breast
### Treatment of Local Recurrence and Metastases

#### Treatment of Local Recurrence:
- R0 resection
- Radiotherapy, chemotherapy after R1 resection

#### Distant Metastases / Unresectable Tumors:
- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford/AGO LOE/GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Radiotherapy, chemotherapy after R1 resection</td>
<td>4 C +/-</td>
</tr>
<tr>
<td>Treatment like soft tissue sarcomas</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Antiangiogenic treatment (e.g. in angiosarcoma)</td>
<td>4 C +/-</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonography (for newly occurring seromas 1 year after implant placement, tumor mass)</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Breast MRI on confirmation of the diagnosis</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Nodal status, PET-CT, bone marrow biopsy</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Cytology of effusion (for newly occurring seromas 1 year after implant placement) with requisition ”r/o BIA-ALCL”</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Lymphoma diagnosis on resection specimen and histological staging (acc. to Clemens 2016)</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Documentation of the implant (manufacturer, size, filling, surface, batch number)</td>
<td>5 D ++</td>
</tr>
</tbody>
</table>
Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Treatment -

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant removal and complete capsulectomy including tumor removal</td>
<td>3a  C  ++</td>
</tr>
<tr>
<td>Removal of suspicious lymph nodes, no routine sentinel-node biopsy, no axillary dissection</td>
<td>4  D  ++</td>
</tr>
<tr>
<td>Polychemotherapy (e.g., CHOP) when extracapsular tumor infiltration</td>
<td>4  D  +</td>
</tr>
<tr>
<td>Radiation for unresectable tumors or R1</td>
<td>5  D  +/-</td>
</tr>
<tr>
<td>Reconstruction after 1 year disease-free interval</td>
<td>5  D  +</td>
</tr>
</tbody>
</table>
Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Summary of the management (acc. to Noah 2017)

1. Periprosthetic seroma or tumor mass > 1 year after implant placement
   - Exclude trauma or infection
     - Ultrasound / sonography
       - Seroma: aspiration and cytology (when suspicious: CD30-IHC)
       - Suspicious: Operative exploration with biopsy of the capsule
       - +ALCL
       - Tumor mass
         - Tumor board discussion
         - Tumor board discussion
         - Complete operative capsulectomy, tumor excision according to oncological standards
         - Lymph node removal in case of suspicion, no new implants, possibly also contralaterally
         - Complete Resection R0
         - R1 or positive lymph nodes
           - Clinical follow-up. Ultrasound and CT every 6 months for 2 years, then annually for 5 years
           - Chemotherapy; CHOP, possibly Immunotherapy
           - +/- Radiatiotherapy

2. Confirmed ALCL cases
   - Tumor board discussion
     - Complete operative capsulectomy, tumor excision according to oncological standards
     - Lymph node removal in case of suspicion, no new implants, possibly also contralaterally
     - Radiation therapy
     - Tumor board discussion

Further Information
References
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:
Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

Screened guidelines:

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

References:

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).

References:


**Prognosis in young women**

3. Gonzalez-Angulo AM et al., Women age < or = 35 years with primary breast carcinoma: Disease features at presentation. Cancer 2005;103: 2466-2472
Chemotherapy in young women

1. Aebi S. Special issues related to the adjuvant therapy in very young women. Breast 2005, 14: 594-599 (Review)

Endocrine therapy in young women

2. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381,805–816
4. Love RR, Laudico AV, Van Dinh N, Allred DC, Uy GB, Quang le H, Salvador JD, Siguan SS, Mirasol-Lumague MR, Tung ND, Benjaafar N, Navarro NS Jr, Quy TT, De La Peña AS, Dofitas RB, Bisquera OC Jr, Linh ND, To TV, Young GS, Hade EM, Jarjoura D. Timing of adjuvant surgical oophorectomy in the menstrual cycle and

Benefit from trastuzumab


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


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


Genetic and fertility counselling

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 lifestyle of the industrialized western world is thus causing an increase in breast cancer incidence.

Moreover, breast cancer incidence is also increasing with age. Pregnant breast cancer patients have an average age of about 32-38 years. Given the increasing average age of pregnant women, the co-incidence of a breast cancer diagnosis with the patient also being pregnant or nursing is becoming more frequent. This fact urgently needs to be acknowledged and accepted by physicians since the diagnosis of breast cancer is frequently being delayed in pregnancy. The average time interval between first symptoms and a definite diagnosis is about 5-15 months. Thus, the diagnosis is typically made at a later stage than outside of pregnancy. This delayed diagnosis is most likely one of the main reasons for the fact that overall survival of pregnant breast cancer patients is worse than that of non-pregnant breast cancer patients even though their stage-adapted prognosis is similar. As a consequence, we not only recommend that pregnant or nursing women need to examine their breast on a regular basis but also that clinical examination of breasts and loco-regional lymph nodes should be part of routine medical care during pregnancy and nursing period.

Another reason for the delayed diagnosis next to “simply not thinking about it” is the reluctance to order appropriate imaging and diagnostic test during pregnancy. Pregnancy or nursing period are no reason for delaying appropriate diagnostic work-up of a suspicious lesion. The same imaging techniques as in non-pregnant women are available. Breast ultrasound will not harm the fetus. Moreover, mammography can also be used if needed, since the danger of too much radiation for the fetus can be overcome by appropriate protective measures. MRI does not have the danger of radiation but experiences with pregnant breast tissue is limited and interpretation may be difficult. Moreover, the position in the MRI may not be acceptable for most pregnant women. Thus, there is no reason to replace an indicated mammography by an
MRI in pregnant patients. Physiological changes in pregnant or nursing breasts cause an increased false-positive rate in imaging procedures. Thus, in pregnant or nursing women, every suspicious palpable tumor definitely needs to be submitted to a histological diagnosis. As in non-pregnant patients, this can be done by minimal invasive techniques such as core or vacuum biopsies under local anesthesia. An open biopsy is only indicated in situations where minimal invasive procedures may not allow a definite diagnosis. In addition, pregnant women as well as their physicians may be more reluctant towards an open biopsy than towards a minimal invasive procedure, thus increasing again the danger of a delay in diagnosis. It is important to make the pathologist aware of the concurrent pregnancy or nursing period in order to avoid pregnancy-associated diagnostic histological changes to cause any diagnostic difficulties or even false-positive findings.

After diagnosis, therapy recommendations follow treatment outside of pregnancy with a few modifications:
Therapeutic radiation of the breast is contraindicated during pregnancy so that a mastectomy would theoretically be the surgical method of choice. However, since adjuvant chemotherapy may be indicated in most cases anyway, the beginning of a radiation therapy may automatically be delayed by a few months thus allowing the pregnancy to reach (almost) full term by the end of chemotherapy. Thus, after delivery, radiation therapy is of course possible and thus breast conserving therapy is a valid option in breast cancer during pregnancy.

In general, chemotherapy can only be applied after the 12th week of pregnancy, i.e. after organogenesis. After the first trimester, chemotherapy does not cause an increased rate of malformations. Yet, there is an increased risk for growth retardation, premature labour, premature delivery, and intrauterine fetal death. Little is known about gonade development of and about the risk for malignancy in the children who were subjected to chemotherapy while still in utero. Indication for chemotherapy follows the guidelines for non-pregnant patients. Yet, one has to consider the individual teratogenic potential of the different chemotherapeutics and plan the delivery date accordingly. Among the most frequently used chemotherapeutics in breast cancer, antimetabolites such as methotrexate (or 5-fluorouracil) should not be used due to their teratogenic potential. For anthracyclines, there is no evidence for major complications. FEC, EC and Epi weekly are safe combinations. Undertreatment should be avoided. There is growing evidence that the use of taxanes is safe. So far, no major complications have been reported. The same is probably true for vinorelbine. Which is possible cytotoxic agent in pregnant metastatic breast cancer patients. Dose-dense chemotherapy does not appear to increase the risk of fetal or maternal complications, but is not recommended at the moment. In conclusion, pregnancy is not a reason for withholding an indicated chemotherapy – the timing however, should take the delivery date into account.
Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot be recommended.
Results of studies of bisphosphonates in pregnant animals have shown maternal toxicity, fetal underdevelopment, 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.

References:

Outcome information (e.g. GBG registry):


Statement: Breast imaging & biopsy like in non-pregnant


Statement: Staging: ultrasound, chest X-ray if indicated

Statement: Surgery like in non-pregnant patients


Statement: „Sentinel node biopsy“ during pregnancy


Reviews

1. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
Breast Cancer During Pregnancy – Neo(adjuvant) Therapy(6/38)

No further information

References:

In general


Statement: Radiotherapy during pregnancy


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


Statement: Anthracyclines: AC, EC

7. Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy: Cognetti F, Bruzzi P, De Placido S, et al. Epirubicin and cyclophosphamide (EC) followed by paclitaxel (T) versus fluorouracil, epirubicin and cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the gruppo Italiano mammella (GIM)-2 randomized phase III study. SABCS 2013: S5-06

Statement: Taxanes


Statement: MTX (e.g. CMF)


Statement: Endocrine treatment


Statement Trastuzumab during pregnancy


Statement Bisphosphonate during pregnancy


General information: Chemotherapy during pregnancy

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.

References:

In general


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

Statements: Delivery mode like in non-pregnant; Avoid delivery ≤ 3 weeks from prior chemotherapy


Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities

1. Williams Obstetrics lecture book
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 proposed additional effects.

References:

In general


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


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).

Review articles


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:

Further information:

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

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

References:


Statement: Treatment according to standard


Statement: Surgery similar to „younger“ age


Statement: Endocrine treatment (endocrine resp.)


Statement: Chemotherapy in pts. < 70 years


Statement: Chemotherapy in pts. > 70 years:


Statement: Radiotherapy

Recently the long term results of a randomized phase 3 trial investigating the role of radiotherapy in elderly patients with breast conserving was reported. Patients 70 years or older with a clinically negative axilla, T1 tumors, breast conserving surgery, and hormone receptor positive tumor were randomized to Tamoxifen and radiation or to tamoxifen alone. Half of the pts were older than 75 years and around 60% had no axillary surgery. Distant disease free survival and overall survival at 10 years were without significant difference between the groups. Local relapse was rare however higher in the no radiation arm (Breast: 2% vs 9%; Axilla: 0% vs 3%).
In a selected low risk population (T1, N0,) in elderly patients (< 70 years) with ER positive disease radiotherapy may be omitted when endocrine treatment with tamoxifen is planned.

2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5

Statement: Trastuzumab

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.

References:

1. Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
2. Audisio RA et al When reporting on older patients with cancer, frailty information is needed Ann Surg Oncol 2011; 18: 4-5
3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).

Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):


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


Statement: No radiotherapy (> 70 y, pT1, pN0, ER+)

5. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.

Statement: Hypofractionated radiotherapy

Statement: No chemotherapy > 70 years and negative risk benefit analysis

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 covered by a gynecomastia. Ultrasound seems more effective.

Surgery:
Wide excision in male breast cancer will almost always include resection of the nipple due to the small amount of breast tissue, and there is some evidence that this is not the most effective method of local control. To establish axillary status in clinically node-negative cases evidence is building up of the accuracy and low morbidity associated with sentinel-node biopsy in women. The technique has also been used in men with similarly encouraging results and sentinel node biopsy will probably become standard practice in the future for node-negative male breast cancer.

Genetic counselling:
Approximately 3-5% of female breast cancers are thought to result from autosomal dominant inheritance, particularly BRCA1 and BRCA2 mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in BRCA2 than BRCA1 families. In a southern Californian population, there were no BRCA1 mutations in 54 patients with male breast cancer, whereas there was a BRCA2 mutation in two (4%) patients. In 94 patients in the UK there were no germline BRCA1 mutations, but five (6%) patients had BRCA2 mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations 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:


General:


Statement: Diagnostic work up as in women
Statement: Mammography


Statement: Ultrasound


Statement: Standard-surgery: Mastectomy – men


Statement: Sentinel-node excision (SNE)


Statement: Radiotherapy as in women (consider tumor breast relation!)


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
Statement: Screening for 2nd malignancies according guidelines


Statement: Systemic therapy


Review articles

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


Statement Trastuzumab


Statement endocrine therapy


Statement palliative chemotherapy

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++)

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].

References:

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

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


Statement: Staging


Statement: Preoperative chemotherapy


Statement: Regimens as in non-inflammatory BC

Statement: in HER2 positive disease addition of trastuzumab


Statement: in HER2 positive disease addition of trastuzumab and pertuzumab


Statement: in HER2 negative disease addition of bevazizumab


Statement: Mastectomy after chemotherapy


Statement: Sentinel lymph node


Statement: Radiotherapy

Statement: Postoperative systemic therapy as in non-inflammatory BC


Reviews

4. Brouwers B et al. Clinicopathological features of inflammatory versus noninflammatory locally advanced nonmetastatic breast cancer
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).

References:

Guidelines:

Reviews:


Pathology


Outcome

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 ≤ 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).

References:

Statement: Mammography / Breast ultrasound/ Breast MRI

**Statement: Staging**


**Statement: PET**

Axillary Metastasis in Occult Breast Cancer (CUP-Ax) - Pathology - (19/38)

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)


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, Varadachary 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).


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 unknown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C/+/-]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% (p<0.001) (Barton 2011), and a trend towards reduced ipsilateral breast tumour recurrence in patients who received radiotherapy was observed in another study (Masinghe 2011).

References:

Guidelines:


Reviews:


Statement: Axillary dissection


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

Statement: Breast irradiation if breast MRI is negative


Statement: Systemic treatment according N+ tumor


Paget’s Disease of the Breast (21/38)

Further information:

Paget’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 Paget’s disease, the underlying malignancy of the breast should be sought for and treated accordingly. Paget’s disease and the associated breast cancer usually is a HER2-positive disease.

References:

Clinical Presentation:

Pathology and Immunohistochemistry

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

No further information

References:

Imaging:


Pathology:

Surgical Treatment of Paget’s disease associated with breast tumor (invasive carcinoma or DCIS):


Treatment of isolated Pagets’s disease


Statement: Sentinel-node excision (SNE)

**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).

*References:*

**Review**


**Pathology and Outcome**


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

*No further information*

**References:**

**Imaging**


**Core biopsy**


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).

References regarding surgical margins:


Other references regarding operative management and prognosis of Phyllodes Tumors.


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 biopsy is not recommended (Chen 2005, Mishra 2013).


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 phyllloides 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.


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

The treatment of local recurrent disease remains unsuccessful in most malignant phyllumes 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).


Statement: Adjuvant radiotherapy, if \( T \geq 2 \text{cm} \) (BCT) or \( T \geq 10 \text{cm} \) (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).

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


Statement: Radiotherapy, chemotherapy after R1 resection

Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas

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.

References:

Reviews

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).

References:

Imaging

Pathology


Prognostic Factors

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.

References:

Surgery

Adjuvant Treatment (Chemotherapy, Radiotherapy)


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 syndrome 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.

References:


Secondary Angiosarcoma of the Breast – Therapy (33/38)

No further information

References:

Surgery


Adjuvant Chemotherapy


Adjuvant Radiotherapy

**Adjuvant Hyperthermia**


**Further References:**

3. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer 2001; 92: 172-180
Angiosarcoma of the Breast – Treatment of Local Recurrence and Metastases (34/38)

No further information

References:

Treatment of local recurrences


Treatment of metastatic and non-resectable tumors

Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) (35/38)

Further information:

Breast implant-associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a rare cancer 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.

References:

Reviews

Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Diagnosis 36/38

Further information:


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.

References:

Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Treatment (37/38)

**Further information:**


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.

**References:**


No further information

No references
Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Breast Cancer
Follow-Up
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

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
Breast Cancer Follow-Up
Objectives

- Improve quality of life
- Improve physical performance
- Reduce therapy related side effects as osteoporosis, cardiac failure, fatigue, neurotoxicity, lymphedema, sexual disorders, cognitive impairment
Breast Cancer Follow-Up Objectives

- Re-evaluation of current adjuvant therapy
  - incl. monitoring of compliance with endocrine therapies

- Pro-active improvement of compliance:
  - Patient information about efficacy data of 5-10 year endocrine therapy
  - Early therapy of side effects (sports, NSAIDs, vitamin D / calcium)
Breast Cancer Follow-Up Objectives

- Psycho-social aspects of support and counseling
  - Pregnancy, contraception, sexuality, quality of life, menopausal symptoms, fear for recurrence
- Second opinion on primary therapy
  4    C     +
- General counseling (genetics, HRT, prophylactic surgery, breast reconstruction)
  2c   B     ++
  2c   C     +
Breast Cancer Follow-Up Objectives

Intervention with regard to co-morbidities and life-style risks in order to reduce negative effects on disease course

- **Treatment of type II-diabetes**
  (>25% undetected DM in postmenopausal BC patients)
  
- **Weight intervention**
  (if BMI <18.5 and >40)
  
- **Reduction of dietary intake** (at least 15% calories from fat)
  in HR neg. breast cancer patients is associated with improved overall survival
  
- **Avoid Smoking**
  (bc related mortality 2 x and BC unrelated mortality 4 x elevated)
  
- **Reduce alcohol consumption below 6 g/d**
  
- **Moderate sport intervention when physical activity was reduced before**

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of type II-diabetes</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Weight intervention</td>
<td>2a B +</td>
</tr>
<tr>
<td>Reduction of dietary intake</td>
<td>2b B +</td>
</tr>
<tr>
<td>Avoid Smoking</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Reduce alcohol consumption below 6 g/d</td>
<td>2b B +</td>
</tr>
<tr>
<td>Moderate sport intervention when physical activity was reduced before</td>
<td>1b A ++</td>
</tr>
</tbody>
</table>
Follow-up Objectives
Reported by Patients

- Examination of the breast
- Reassurance
- Guidance of patients, answering questions
- Evaluation of treatment and treatment of side effects
- Psychosocial support

Oxford LoE 4 C
Routine Follow-Up Examinations in Asymptomatic Patients

Tests:

- History (specific symptoms)  
  - Oxford / AGO LoE / GR: 1a A ++

- Physical examination  
  - Oxford / AGO LoE / GR: 1a B ++

- Breast self-examination  
  - Oxford / AGO LoE / GR: 5 D +

- Mammography  
  - Oxford / AGO LoE / GR: 1a A ++

- Sonography of the breast  
  - Oxford / AGO LoE / GR: 2a B ++

- Routine MRI of the breast  
  - Oxford / AGO LoE / GR: 3a B +/-

- MRI of the breast in case of inconclusive conventional imaging  
  - Oxford / AGO LoE / GR: 3b B +

- Pelvic examination  
  - Oxford / AGO LoE / GR: 5 D ++

- DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI  
  - Oxford / AGO LoE / GR: 5 D +
Routine Follow-Up Examinations in Asymptomatic Patients

- 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 -
Local recurrence & in-breast recurrence:

- Incidence 7–20% (depending on time of F/U)
- Breast self-examination
- Physical examination, mammography & US
- Magnetic resonance imaging (MRI)
Early Detection of Potentially Curable Events

Contralateral breast cancer:

- Rel. risk: 2,5–5
- Incidence: 0,5–1,0 % / year

- Breast self-examination
- Physical examination, mammography & US
- Routine breast MRI

Oxford / AGO LoE / GR

5 D +
1a A ++
5 D -
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
  - 5D++
- Pelvic examination and PAP smear
  - 5D++
- Routine endometrial ultrasound / biopsy
  - 1bB-
# 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)

<table>
<thead>
<tr>
<th>Clinical follow-up</th>
<th>Follow-Up*</th>
<th>Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years after primary therapy</td>
<td>1 2 3</td>
<td>4 5</td>
</tr>
<tr>
<td>History, physical examination, counseling</td>
<td>inv.: every 3 months</td>
<td>inv.: every 6 months</td>
</tr>
<tr>
<td>Self-examination</td>
<td></td>
<td>monthly</td>
</tr>
<tr>
<td>Imaging modalities and biochemistry</td>
<td>indicated only by complaints, clinical findings or suspicion of recurrence</td>
<td></td>
</tr>
<tr>
<td>Mammo-graphy and additionally sono-graphy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCT**</td>
<td>ipsilat.: every 12 months</td>
<td>on both sides: every 12 months</td>
</tr>
<tr>
<td></td>
<td>contralat.: every 12 months</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td></td>
<td>contralateral every 12 months</td>
</tr>
</tbody>
</table>

* Continued follow-up visits if still on adjuvant treatment

** In pts with breast-conserving therapy (BCT): First mammography 1 year after initial mammography or at least 6 months after completion of radiotherapy
Breast Cancer Follow-up
Duration and Breast Nurses

➢ Duration of follow-up
  ➢ until 5 yrs
  ➢ until 10 yrs

➢ Surveillance by specialized breast nurses

Oxford / AGO
LoE / GR

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

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

- Intrinsic typing of breast cancer leads to subgroups with different course of disease. Thus, postoperative surveillance should be adapted to specific time-dependent hazards of recurrence.

- ER-positive patients have stable risk over many years requiring long term surveillance.

- However, patients with HER2-positive disease and TNBC have more risk in the early phase of follow-up and should therefore receive more intense surveillance in the first years of follow-up.

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

References:


Statement: Psycho-social aspects


Statement: risk factors of mortality after loco-regional recurrence

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

No further information

References:

Statement: Obesity, physical activity and quality of life


Statement: Obesity and breast cancer prognosis


Statement: Lymphedema

Statement: sexual disorders and cognitive impairment:


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


2. Neven P, Markopoulos C, Tanner MME et al.: The Impact of Educational Materials on Compliance and Persistence with Adjuvant Aromatase Inhibitors: 2 Year Follow-Up and Final Results from the CARIATIDE Study. SABCS 2011 [P5-16-02].


Statement: Early Detection of Distant Disease

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

*No further information*

**References:**

**Statement: Early Detection**


Statement: Psycho-social aspects

Statement: prophylactic surgery

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

No further information

References:

Statement: Early Detection


Statement: Psycho-social aspects


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

**Weight intervention**

**Moderate sport intervention when physical activity was reduced**
Follow-up Objectives – Reported by Patients (8/16)

No further information

References:

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

No further information

References:

Statement: History (specific symptoms)

**Statement: Physical examination**


**Statement: Breast self-examination**

**Expert Opinion**

**Statement: Mammography**

Statement: Sonography of the breast


Statement: MRI of the breast in case of inconclusive conventional imaging

Statement: Pelvic examination

Expert Opinion


Statement: Dxa scan

Expert Opinion

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

No further information

References:

Statement: Magnetic resonance imaging (MRI) of the breast


Statement: Routine biochemistry (incl. tumor markers)

Statement: Ultrasound of the liver


Statement: Bone scan

Statement: Chest X-ray


Statement: CT of chest, abdomen and pelvis

Statement: Detection of isolated/circulating tumor cells


Statement: PET

Statement: Whole body MRI


Early Detection of Potentially Curable Events (11/16)

No further information

References:

Statement incidence


Statement breast self examination

Statement physical examination, mammography & US


Early Detection of Potentially Curable Events (12/16)

No further information

References:

Statement risk and incidence


Statement breast self examination

Statement physical examination, mammography & US


Statement: Risk according to intrinsic subtype

Early Detection of Potentially Curable Events (13/16)

No further information

References:

Statement: Risk


Statement: Screening for secondary malignancies according to current guidelines

Statement: Pelvic examination and PAP smear


Statement: Endometrial ultrasound / biopsy

Statement: Marrow neoplasms after adjuvant breast cancer therapy

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

No further information

References:

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

No further information

References:


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

No further information

References:


Loco-Regional Recurrence
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
# Loco-regional Recurrence

## Incidence and Prognosis

<table>
<thead>
<tr>
<th>Localization</th>
<th>Frequency (%)</th>
<th>5-y. Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral recurrence(^1)</td>
<td>10 (2–20)</td>
<td>65 (45–79)</td>
</tr>
<tr>
<td>(post BCT + irradiation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wall(^1)</td>
<td>4 (2–20)</td>
<td>50 (24–78)</td>
</tr>
<tr>
<td>(post mastectomy)</td>
<td></td>
<td></td>
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<tr>
<td>As above plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supraclavicular fossa(^2)</td>
<td>34%</td>
<td>49% (3-y. OS)</td>
</tr>
<tr>
<td>Axilla:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ALND(^1)</td>
<td>1 (0.1–8)</td>
<td>55 (31–77)</td>
</tr>
<tr>
<td>After SNB(^4)</td>
<td>1</td>
<td>93%</td>
</tr>
<tr>
<td>Multiple localizations(^2)</td>
<td>16 (8–19)</td>
<td>21 (18–23)</td>
</tr>
</tbody>
</table>

Loco-regional Recurrence Staging

Examinations before treatment:

- Tissue biopsy
- Re-assessment of ER, PgR, HER2
- Complete re-staging

<table>
<thead>
<tr>
<th>Examination</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue biopsy</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Re-assessment of ER, PgR, HER2</td>
<td>3b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Complete re-staging</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>
### Increased risk for loco-regional recurrence

- Young age
- Positive microscopic margins (R1) of the primary tumor
- Omitting adjuvant radiotherapy (if indicated)
- Extensive intraductal component
- Vessel invasion
- HER2 positive and triple negative > Luminal B-like
  > luminal A-like
- Number of involved lymph nodes
- Grading (G3)
- Elevated proliferation markers: e.g. Ki67;
- pT (> 2)
  * node negative
- Inflammatory breast cancer
- Medial tumor localisation
- Obesity (Body mass index)
Metaanalysis: TNBC and Local Recurrence


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

<table>
<thead>
<tr>
<th></th>
<th>BCT</th>
<th>vs.</th>
<th>ME</th>
<th>Hazard-ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.75 (0.65-0.87)</td>
<td></td>
<td>ME</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>0.68 (0.60-0.76)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>other subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>1.88 (1.58-2.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>2.12 (1.72-2.62)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>HER2-subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.69 (0.53-0.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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


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

Risk factors for 10 yr. cumulative incidence …:

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

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

...> 5% axillary failure: age < 40; unknown tumor size, 0-7 uninvolved nodes
Metaanalysis: 7174 BCT and 5418 ME


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
### Loco-regional Recurrence

#### Prognostic / Predictive factors

<table>
<thead>
<tr>
<th>Parameters of the locally recurrent tumor to define the risk for re-recurrence</th>
<th>Oxford AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size</strong></td>
<td>2a B</td>
</tr>
<tr>
<td><strong>Multifocality</strong></td>
<td>2a B</td>
</tr>
<tr>
<td><strong>Localisation</strong></td>
<td>2b B</td>
</tr>
<tr>
<td><strong>Negative progesterone receptor</strong></td>
<td>3b B</td>
</tr>
</tbody>
</table>

Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Oxford AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early (&lt;2-3 yrs.) vs. late recurrence</strong></td>
<td>2b B</td>
</tr>
<tr>
<td><strong>LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)</strong></td>
<td>3b B</td>
</tr>
</tbody>
</table>

Predictive factors for treatment considerations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Oxford AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2</strong></td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>ER and PgR</strong></td>
<td>2b B ++</td>
</tr>
</tbody>
</table>
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

- **Mastectomy (aim: R0)**
  - Oxford LoE: 3b
  - AGO GR: B
  - AGO LoE: ++

- **Re-BCS with tumor-free margins (R0)**
  - Oxford LoE: 3b
  - AGO GR: C
  - AGO LoE: +/-

- **Axillary intervention after prior AxDiss if cN0**
  - Oxford LoE: 4
  - AGO GR: C
  - AGO LoE: -

- **SLNE after prior SLNE if cN0**
  - Oxford LoE: 1b
  - AGO GR: B
  - AGO LoE: -

- **Palliative surgery in M1-situation**
  - (e.g. pain, ulceration, psychosocial indication)
  - Oxford LoE: 5
  - AGO GR: D
  - AGO LoE: +

*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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>

- **Curative situation: R0-resection**
- **Palliative situation: Resection of deep parts of the chest wall**
- **Palliative surgery in M1-situation**
  - (e.g. pain, ulceration, psychosocial)
Loco-regional Recurrence after R0-Resection
Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors
- Chemotherapy (consider preoperative)
- In case of HER2 positive disease, chemotherapy + HER2 targeted therapy

Oxford AGO
LoE / GR

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 +
**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

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors
  LoE / GR: 2b B ++

- Chemotherapy (pre- or postoperatively)
  LoE / GR: 2b B ++

- HER2-targeted therapy in HER2-positive tumors (with chemotherapy)
  LoE / GR: 5 D ++
Ipsilateral Recurrence after BCT Radiotherapy

After Re-BCS

- Whole breast irradiation
  (in case adjuvant radiotherapy was not performed)
- Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
  (14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)
- Repeated irradiation (e.g. as brachytherapy) with hyperthermia

Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole breast irradiation (in case adjuvant radiotherapy was not performed)</td>
<td>3b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Radiation of chest wall +/- regional lymph nodes</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Radiation dose escalation (+10%)</td>
<td>3b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Repeated irradiation (e.g. as brachytherapy) with hyperthermia</td>
<td>3a</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Chest-Wall Recurrence after Mastectomy / Axillary Recurrence
Radiotherapy

Chest-Wall Recurrence after Mastectomy
- If no prior postmastectomy radiotherapy
  - Curative situation: irradiation of the chest wall +/- regional lymph nodes
  - Re-irradiation (chest wall + hyperthermia)

Axillary recurrence
Irradiation of axilla after R0-surgery
- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

<table>
<thead>
<tr>
<th>Oxford</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2b</strong></td>
<td><strong>B</strong></td>
</tr>
<tr>
<td><strong>1b</strong></td>
<td><strong>B</strong></td>
</tr>
<tr>
<td><strong>3b</strong></td>
<td><strong>C</strong></td>
</tr>
<tr>
<td><strong>5</strong></td>
<td><strong>D</strong></td>
</tr>
</tbody>
</table>
Loco-Regional Recurrence
Treatment Options in Non Curative Cases

- Concomitant radio-chemotherapy
- Hyperthermia (in centers listed on DKG website)
  - In combination with radiotherapy
  - In combination with chemotherapy
- Intra-arterial chemotherapy
- Photodynamic therapy
- Electrochemotherapy
Loco-regional Recurrence (2/18)

Further information and references:


Guidelines:


Loco-regional Recurrence Incidence and Prognosis (3/18)

Further information:

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

References:


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.

**References:**

**Loco-regional Recurrence Risk Factors at Primary Diagnosis (5/18)**

**Further information:**

Risk factors for IBTR include tumor size, nodal status, estrogen receptor status, molecular subtype, young age, positive microscopic margins, extensive intraductal component, higher grading, vessel invasion multifocality, an extensive intraductal component, and lymphatic vessel invasion. Multivariate analysis stratified by treatment showed that age was an independent prognostic factor for local control. Systemic treatment and radiation therapy significantly reduced local recurrence.

**References:**

Informative for the whole list of factors:


**Statement: Increased risk for loco-regional recurrence**


Statement: Young age


Statement: Positive microscopic margins


Statement: Extensive intraductal component


Statement: Vessel invasion


Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors


Statement: Grading G3


Statement: pT > 2


Statement: pN (N1 vs. N0)


2. www.tumorregister-muenchen.de
Statement: pN (N1 vs. N0) and number of involved lymph nodes

7. Truong PT, Jones SO, Kader HA, Wai ES, Speers CH, Alexander AS, Olivotto IA. Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73(2):357-64, 2009
8. Curr Oncol. 2014 Oct;21(5):e685-90. doi: 10.3747/co.21.2000 Risk factors for locoregional recurrence after postmastectomy radiotherapy in breast cancer patients with four or more positive axillary lymph nodes.Li Q1, Wu S2, Zhou J3, Sun J1, Li F1, Lin Q2, Guan X1, Lin H1, He Z1
Statement: Medial tumor localisation


Statement: elevate proliferation marker, esp. Ki67


Statement: Inflammatory breast cancer


Statement: Nomograms


Statement: Obesity


Recent evidence for Multigene arrays predicting risk for local relapse:

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**


**Statement: Multifocality**


**Statement: Localisation**


Statement: ER-pos/PgR-pos vs ER-pos/PgR-neg or ER-neg/PgR-neg


Statement: Early vs. Late recurrence


LVSI/Grade/ERneg/close margins
Change from close margin to positive margin

Predictive factors for treatment considerations

Statement: HER-2


Statement: ER and PR

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)

Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0


9. Reoperative Sentinel Lymph Node Biopsy is Feasible for Locally Recurrent Breast Cancer, But is it Worthwhile? Ugras S1, Matsen C1, Eaton A3, Stempel M1, Morrow M1, Cody HS 3rd4.

Statement: Palliative surgery in M1-situation

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


Statement: Palliative situation: Resection of deep parts of the chest wall


Statement: Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)

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


Statement: Chemotherapy


Statement: Trastuzumab - based therapy in HER-2 overexpressing tumors

So far, extrapolations from adjuvant HER2-directed studies and from studies in metastatic breast cancer


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


Statement: Chemotherapy (pre- or postoperatively)


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


Statement: Re-irradiation (breast)


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


Statement Re-Irradiation of the chest wall with hyperthermia:


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

No further information

References:

Statement: If no prior postmastectomy radiotherapy


Statement: Re-irradiation (chest wall + hyperthermia)

Statement Axillary recurrence

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


Statement: Hyperthermia + radiotherapy +/- chemotherapy

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

Statement: Photodynamic therapy


Statement: Electrochemotherapy

Endocrine and “Targeted” Therapy in Metastatic Breast Cancer
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
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.
Comparison ER/PR and HER2 Metastasis vs. Primary Tumor

Meta-analysis based on 48 (mostly retrospective) analyses:

Pooled discordance proportions were
- 20% (95% CI 16-35%) for ER
- 33% (95% CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Pooled proportions of tumors shifting from positive to negative and negative to positive were
- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2
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

- GnRHa + Fulvestrant + Palbociclib
- GnRHa + Al + Palbociclib
- GnRHa + tamoxifen (vs. OFS or Tam)
- Ovarian function suppression (OFS)
- Tamoxifen
- GnRHa + Al (first or second line)
- GnRHa + Fulvestrant
- Aromatase inhibitors without OFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRHa + Fulvestrant + Palbociclib</td>
<td>2b B ++</td>
</tr>
<tr>
<td>GnRHa + Al + Palbociclib</td>
<td>5 D +</td>
</tr>
<tr>
<td>GnRHa + tamoxifen (vs. OFS or Tam)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ovarian function suppression (OFS)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b B +</td>
</tr>
<tr>
<td>GnRHa + Al (first or second line)</td>
<td>2b B +</td>
</tr>
<tr>
<td>GnRHa + Fulvestrant</td>
<td>1b B +</td>
</tr>
<tr>
<td>Aromatase inhibitors without OFS</td>
<td>3 D - -</td>
</tr>
</tbody>
</table>
Endocrine Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be preferred in first line.

- Letrozole + Palbociclib
- Fulvestrant 500 mg + Palbociclib
- Fulvestrant 500 mg
- Aromatase inhibitors (3rd generation)*
- Tamoxifen
- Exemestane + Everolimus
- Tamoxifen + Everolimus
- Letrozole + Everolimus
- Fulvestrant + Everolimus
- Fulvestrant 250 mg + Anastrozole
- Repeat prior treatments

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole + Palbociclib</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant 500 mg + Palbociclib</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Aromatase inhibitors (3rd generation)*</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Exemestane + Everolimus</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Tamoxifen + Everolimus</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Letrozole + Everolimus</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant + Everolimus</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant 250 mg + Anastrozole</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Repeat prior treatments</td>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>

*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.
Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab

- Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab
- Bevacizumab plus endocrine treatment as first line therapy for advanced disease

Oxford / AGO LoE / GR

1b B +/-
HER2 Positive and HR-Positive Metastatic Breast Cancer
Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

- Anastrozole plus trastuzumab
- Letrozole plus trastuzumab
- Letrozole plus lapatinib
- Fulvestrant plus lapatinib
- Aromatase inhibitors plus Trastuzumab / Pertuzumab*

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

*Study participation recommended
Concomitant or Sequential Endocrine-Cytostatic Treatment

- **Concomitant endocrine-cytotoxic treatment**
  - May increase response rate and progression free interval but not overall survival
  - May increase toxicity

- **Maintenance endocrine therapy after chemotherapy induced response**
  - Increases progression free interval

Oxford / AGO LoE / GR

Concomitant or Sequential Endocrine-Cytostatic Treatment

- **1b**
  - A
  - -

- **2b**
  - B
  - +
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)

No further information

References:

Comparison ER/PR and HER2 Metastasis vs. Primary Tumor (4/11)

No further information

References:

Endocrine Therapy  General Considerations (5/11)

No further information

References:


Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (6/11)

No further information

References:

GnRHa plus fulvestrant plus palbociclib


GnRHa plus tamoxifen (vs. OFS or tam)

Ovarian function suppression (OFS), tamoxifen


GnRHa plus AI (first or second line)


GnRHa plus fulvestrant

Endocrine Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer (7/11)

No further information

References:

Letrozole and palbociclib (vs. letrozole alone)


Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone)

Fulvestrant 500 mg (vs. anastrozole)


Fulvestrant 500 mg >> 250 mg


Aromatase inhibitors (3rd generation)*


Aromatase inhibitors (3rd generation) (>non-AI)

1. Bonneterre, J, Buzdar, A, Nabholtz, JA, Robertson, JFR, Thuerlimann, B, von Euler, M. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


Exemestane and everolimus (vs. exemestane alone)


Tamoxifen and everolimus


Fulvestrant and everolimus


Letrozole and everolimus

Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab (8/11)

No further information

References

Maintenance of bevacizumab plus endocrine therapy


Bevacizumab plus endocrine treatment as first line


Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients (10/11)

No further information

References

Anastrozole and trastuzumab


Letrozole and trastuzumab


Letrozole and lapatinib


Fulvestrant and lapatinib

AI and trastuzumab/pertuzumab

1. Arpino G, Ferrero J-M, de la Haba-Rodriguez J, Easton V, Schuhmacher C, Restuccia E, Rimawi M. Primary analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer. SABCS 2016, #S3-04
Concomitant or Sequential Endocrine-Cytostatic Treatment (11/11)

No further information

References:

Concomitant endocrine-cytotoxic treatment


Maintenance endocrine therapy after chemotherapy induced response

Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*Substances are only discussed if there is at least published evidence based on one phase III / IIb study available
Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **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
An increase in survival over time in MBC has been shown in some retrospective analyses.

However, patients with MBC today have received more adjuvant treatment and have therefore to be considered more drug resistant.

Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity).

Especially targeted drugs in combination with chemotherapy can induce substantial survival benefits.
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

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017
## Treatment of Metastatic Breast Cancer

### Predictive Factors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td>ER / PR</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>(primary tumor, metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>previous response</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>previous response</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Anti-HER2-drugs</td>
<td>HER2</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>(primary tumor, better metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Bone modifying drugs</td>
<td>bone metastasis</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Any therapy</td>
<td>CTC monitoring</td>
<td>1b A +*</td>
</tr>
</tbody>
</table>

(Other potentially biological factors see chapter „Predictive factors“)

*Within clinical trials*
Cytotoxic Therapy

Goals

Mono-Chemotherapy:
- Favourable therapeutic index
- Indicated in case of:
  - Slow, not life-threatening progression
  - Insensitive to or progression during endocrine therapy

Poly-Chemotherapy:
- Unfavourable therapeutic index
- Indicated to achieve rapid remission in the case of:
  - Extensive symptoms
  - Imminent life-threatening metastases
- Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

Therapeutic index evaluates overall efficacy, toxicity and impact on quality of life
Cytotoxic and Targeted Therapy

- Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities)
- Assess subjective and objective toxicities, symptoms, and performance status repeatedly
- Use dosages according to published protocols
- Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion might be sufficient. In slowly growing disease, longer intervals are acceptable.
Cytotoxic Therapy
Duration

As long as therapeutic index remains positive

- Treatment until progression

- Treatment until best response

- Change to alternative regimen before progression

- Stop therapy in case of
  - Progression
  - Non tolerable toxicity

<table>
<thead>
<tr>
<th>Oxford / AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>1c</td>
<td>A</td>
</tr>
</tbody>
</table>
The choice of cytotoxic drugs to be used depends on:

- ER / PR, HER2; combination with biologicals
- Previous treatments (and their toxicities)
- Disease-free interval after end of adjuvant treatment
- Aggressiveness of disease and localization of metastases
- Estimated life expectancy
- Co-morbidities (including organ dysfunctions)
- Patients preference and expectations
### MBC HER2-negative/HR-positive Cytotoxic 1st-Line Therapy*

#### Monotherapy:
- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, mitoxantrone (A)
  - Peg. liposomal doxorubicin (A<sub>lip</sub>)
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

#### Polychemotherapy:
- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- T + gemcitabine after adj. A
- A + C or A<sub>lip</sub> + C

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

*In ER pos. disease only if endocrine therapy is not or not anymore indicated*
MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel q1w</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Docetaxel q3w</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Docetaxel + Peg-liposomal Doxo</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

*Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation
### MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental therapies within studies</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b B ++</td>
</tr>
<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>2b B +</td>
</tr>
<tr>
<td>Taxane re-challenge*</td>
<td>2b B +</td>
</tr>
<tr>
<td>Anthracycline re-challenge*</td>
<td>3b C +</td>
</tr>
<tr>
<td>Metronomic therapy (eg. cyclophos. + MTX)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine</td>
<td>1b B -</td>
</tr>
</tbody>
</table>

*At least one year disease-free after adjuvant treatment*
Triple Negative Metastatic Breast Cancer

- Experimental therapies within studies

- Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC
  - Carboplatin (vs. Docetaxel)
    - in gBRCA mutation
  - Gemcitabine/Cisplatin (vs. Gem/Pac)
  - Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)
  - Bevacizumab added to first line cytotoxic therapy

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin vs. Docetaxel</td>
<td>1b^a B +/-</td>
</tr>
<tr>
<td>Carboplatin vs. Docetaxel in gBRCA mutation</td>
<td>1b^a B +</td>
</tr>
<tr>
<td>Gemcitabine/Cisplatin vs. Gem/Pac</td>
<td>1b A +</td>
</tr>
<tr>
<td>Nab-Paclitaxel/Carboplatin vs. Carbo/Gem</td>
<td>2b^a B +</td>
</tr>
<tr>
<td>Bevacizumab added to first line cytotoxic therapy</td>
<td>1b B +</td>
</tr>
</tbody>
</table>
Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line in combination with:</td>
<td>1b  B  +</td>
</tr>
<tr>
<td>Paclitaxel (q1w)</td>
<td>1b  B  +</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b  B  +/-</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>2b  B  +/-</td>
</tr>
<tr>
<td>Nab-Pac</td>
<td>1b  B  +/-</td>
</tr>
<tr>
<td>Docetaxel (q3w)</td>
<td>1b  B  +/-</td>
</tr>
<tr>
<td>Cap+Bev as maintenance after Doc+Bev</td>
<td>1b⁰  B  +/-</td>
</tr>
</tbody>
</table>

| 2nd line in combination with: | 1b  B  +/- |
| Taxanes | 1b  B  +/- |
| Capecitabine | 1b  B  - |
| Gemcitabine or vinorelbine | 1b  B  - |

| 2nd line as treatment through multiple lines | 1b  B  - |
First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

- Docetaxel + trastuzumab + pertuzumab
- Paclitaxel (wk) + trastuzumab + pertuzumab
- Nab-Paclitaxel + trastuzumab + pertuzumab
- Vinorelbine + Trastuzumab + Pertuzumab
- T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)
- 1\textsuperscript{st} line chemotherapy* + trastuzumab
- Trastuzumab mono
- Taxanes + lapatinib
- Taxanes + trastuzumab + everolimus
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1b A ++</th>
<th>2b B ++</th>
<th>3b\textsuperscript{a} C +</th>
<th>3b B +</th>
</tr>
</thead>
</table>
| *Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel
**see chapter Endocrine +/- targeted
2nd line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)

- T-DM 1
- TBP: 2nd line chemotherapy + trastuzumab
- TBP: 2nd line chemotherapy + trastuzumab + pertuzumab
- Any other 2nd line chemotherapy* + trastuzumab + pertuzumab
  - Taxane + trastuzumab + pertuzumab
  - Capecitabine + trastuzumab + pertuzumab
- Capecitabine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)

* e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b A ++</td>
</tr>
<tr>
<td>TBP: 2nd line chemotherapy + trastuzumab</td>
<td>2b B +</td>
</tr>
<tr>
<td>TBP: 2nd line chemotherapy + trastuzumab + pertuzumab</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>Any other 2nd line chemotherapy* + trastuzumab + pertuzumab</td>
<td>5 D +</td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b B +</td>
</tr>
</tbody>
</table>
Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

Pretreatment with Trastuzumab

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

Neither data for patients pretreated with trastuzumab and pertuzumab nor data for treatment beyond progression available.

- Experimental anti-HER2-regimen
- For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine + lapatinib</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b</td>
<td>+/-</td>
</tr>
<tr>
<td>Chemotherapy + trastuzumab (“treatment beyond progression“)</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab + pertuzumab</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)</td>
<td>1b</td>
<td>+/-</td>
</tr>
</tbody>
</table>

| Further Information
| References
| Oxford / AGO LoE / GR
| 5 | D | + |
Lapatinib in HER2-positive Metastatic Breast Cancer

In combination with

- Trastuzumab for heavily pre-treated pts (HR negative)
  - Oxford / AGO LoE / GR: 2b B +

- Paclitaxel in 1\textsuperscript{st} line
  - Oxford / AGO LoE / GR: 1b B +/-

- Capecitabine in > 2\textsuperscript{nd} line
  - Oxford / AGO LoE / GR: 1b B +

- Vinorelbine
  - Oxford / AGO LoE / GR: 2b B +/-

- AI in ER positive disease
  - Oxford / AGO LoE / GR: 2b B +/-

- In patients with brain metastases (radioresistance) in combination with capecitabine
  - Oxford / AGO LoE / GR: 2b B +/-
Immunodiagnostic Tests and Immunotherapy*

Immunodiagnostic tests:
Immunological parameters in peripheral blood

Local immunotherapy

- Imiquimod topically for skin metastases

Systemic immunotherapy - including items below – only within clinical trials:

- HER2-vaccination in high risk population
- Immunomodulation (e.g. addition of Nov-2 to AC –T)
- Dendritic cell intradermal vaccination
- Active vaccination
- Passive vaccination
- Therapy with oncolytic viruses
- Cytokines
- Checkpoint inhibitors (PD1; PDL-1;…)

*Study participation recommended
Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/19)

No further information

References:

International consensus

Update since 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).
Disease-Free and Overall Survival in Metastatic Breast Cancer (3/19)

No further information

References:

International consensus


Increase


Multiple lines

Endocrine resistance in metastatic breast cancer (4/19)

No further information

References:

International consensus

Treatment of Metastatic Breast Cancer - Predictive Factors (5/19)

No further information

References:

CTC monitoring


Cytotoxic Therapy Goals (6/19)

No further information

References:

International consensus


Combination vs single agent


Cytotoxic and Targeted Therapy (7/19)

No further information

References:

International consensus

Cytotoxic Therapy Duration (8/19)

No further information

References:

International consensus


Change to alternative regimen before progression:

Treatment until progression


Chemotherapy for MBC – General Considerations: Drug Selection (9/19)

No further information

References:

International consensus


Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better


Limitations of palliative chemotherapy

MBC HER2 negative Cytotoxic 1st-Line Therapy (10/19)

No further information

References:

International consensus


Single Agents


**Polychemotherapy**

**Metaanalysis:**


Cochrane analysis containing taxane based regimens


**After anthracycline treatment two studies could show a survival benefit:**


Doxorubicin/docetaxel vs. Doxorubicin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL:


Other combinations:


**MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment** (11/19)

*Further information and references:*

**International consensus**


**Cochrane analysis taxane-containing regimens for metastatic breast cancer**


**Nab-paclitaxel**


**Erubilin**


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 breasts 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 advantage from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.
MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (12/19)

No further information

References

International consensus


Capecitabine:


Eribulin


**Taxane re-challenge**


**Anthracycline re-challenge**


**Metronomic chemotherapy**


**Gemcitabine + cisplatin / carboplatin**


**Gemcitabine + capecitabine**


**Gemcitabine + Vinorelbine:**


**Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (13/19)**

*Further information and references:*

**International consensus**


**Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:**


**Gemcitabin/Cisplatin (vs. GemPac)**

Nab-Paclitaxel / Carboplatin:


Bevacizumab as first-line therapy

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (14/19)

Further information and references:

International consensus


First-line chemotherapy and bevacizumab:


Taxane and bevacizumab first-line

Nab-Paclitaxel and bevacizumab first-line:


Capecitabine and bevacizumab first-line


Cap+Bev as maintenance after Doc+Bev:


Second-line chemotherapy and bevacizumab:


2nd line as treatment through multiple lines:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (15/19)

No further information

References:

International consensus


ASCO recommendation:


Docetaxel + trastuzumab + pertuzumab

Paclitaxel weekly + trastuzumab + pertuzumab


Nab-Paclitaxel + trastuzumab + pertuzumab


Vinorelbine + trastuzumab + pertuzumab


T-DM1 after rapid progress


1st line chemotherapy + trastuzumab


Trastuzumab mono


Taxanes+ lapatinib


Taxane + trastuzumab + everolimus

1. Hurvitz SA et al., Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial, Lancet Oncol. 2015;16(7):816-29

Trastuzumab + aromatase inhibitors (if ER+)

Lapatinib + aromatase inhibitors (if ER+)

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab) (16/19)

No further information

References:

International consensus


ASCO recommendation:

T-DM1


TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)


TBP: 2nd-Line chemotherapy + Trastuzumab + pertuzumab (Treatment beyond progression)

Any other 2nd-Line chemotherapy + trastuzumab + pertuzumab


Taxane + trastuzumab + pertuzumab


Capecitabine + Trastuzumab + Pertuzumab


Capecitabine + lapatinib


3. When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.


**Trastuzumab + lapatinib**


Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (17/19)

No further information

References:

International consensus


ASCO recommendation:

T-DM1


Capecitabine + Lapatinib


Vinorelbine + Lapatinib:


Trastuzumab + lapatinib vs lapatinib


TBP: 2nd-line chemotherapy + trastuzumab


Trastuzumab + pertuzumab


Vinorelbine + Trastuzumab + Everolimus

Lapatinib in HER2-positive Metastatic Breast Cancer (18/19)

No further information

References:

Trastuzumab + lapatinib vs lapatinib


Taxanes+ lapatinib


Capecitabine + Lapatinib


Vinorelbine + Lapatinib:


Lapatinib + aromatase inhibitors (if ER+)

Brain metastases (radioresistance)

Immunodiagnostic Tests and Immunotherapy (19/19)

No further information

No references
Osteo-oncology and Bone Health
Osteoonecology and Bone Health

- **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

- 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 ++
Denosumab in Metastatic Breast Cancer

- 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 +/-
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

## Bone Modifying Agents for the Therapy of Bone Metastases

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing Schedule</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate PO 1600 mg daily</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Clodronate IV 1500 mg q3w / q4w</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Pamidronate IV 90 mg q3w / q4w</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate IV 6 mg q3w / q4w</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate PO 50 mg daily</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Zoledronate IV 4 mg</td>
<td>q4w</td>
<td>1a A +</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. q4w</td>
<td></td>
<td>1a A ++</td>
</tr>
<tr>
<td>Denosumab 120 mg s.c. q12w</td>
<td></td>
<td>4 C -</td>
</tr>
<tr>
<td>Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis</td>
<td></td>
<td>5 D - -</td>
</tr>
</tbody>
</table>
Skeletal Metastases
Treatment with Radionuclids

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisite: hot spots in the bone scintigraphy)
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat
  - $^{153}$Samarium
  - $^{89}$Strontium
  - $^{223}$Radium

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.
Metastatic Bone Disease
of the Spine

Indications for surgery

- Spinal cord compression
  - With progressive neurological symptoms
  - With pathological fractures
- Instability of the spine
- Lesions in pre-irradiated parts of the spine

Oxford LoE: 2b  GR: C  AGO: ++
Bone Metastases
Acute Spinal Cord Compression / Paraplegia

- 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!
Surgery for Bone Metastases
Technical Aspects

Spine and limbs

Oxford LoE: 3b  GR: C  AGO: +

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprothesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)

*Study participation recommended
Metastatic Bone Disease: Radiotherapy (RT)

**Bone metastases**

- 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

Recurrent bone pain in pre-irradiated parts of the skeleton

- Single dose RT* 3b C ++
- Fractionated RT* 3b C +
- Radionuclid therapy 3b C +
- Magnetic resonance-guided focused ultrasound 1b B +
- Radiofrequency ablation 4 C +
- Cryoablation 4 C +

*Dosing and fractionation depending on location, interval from first RT, and dose and fractionation of first radiotherapy.
Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db)

- 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 2b
  (absolute risk of 11 per 10,000 person years of BP use)
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
Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Recommendation Levels</th>
<th>Grade</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate (oral)</td>
<td></td>
<td>1a A</td>
<td>+</td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td></td>
<td>1a B</td>
<td>+/-</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminobisphosphonates (iv or oral)</td>
<td></td>
<td>1a A</td>
<td>+</td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td></td>
<td>1a B</td>
<td>+/-</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab (60 mg s.c., q6mo)</td>
<td></td>
<td>1b a</td>
<td>B +/-</td>
</tr>
</tbody>
</table>
Dosage of Adjuvant Bisphosphonates for Improvement of Survival

- **Non-Aminobisphosphonates:**
  - Clodronate po 1600 mg/d (Bonefos/ Clodronic acid)
  - Clodronate po 1040 mg/d (Ostac)

- **Aminobisphosphonates:**
  - Zoledronate iv 4 mg/6 m (Zometa/ Zoledronic acid)
  - Ibandronate po 50 mg/d (Bondronat/ Ibandronic acid)
  - Pamidronate po (orally not available in most countries)
  - Risedronate po 35 mg/w*(Actonel/ Risedronic acid)
  - Alendronate po 70 mg/w (Fosamax/ Alendronic acid)

  Optimal duration yet to be defined; in adjuvant studies duration of BP treatment varied from 2–5 years

Aminobisphosphonates include:
Zoledronic acid (65 %), oral ibandronate (24 %), oral pamidronate (8 %), oral risedronate (2 %), oral alendronate (1 %) (data from EBCTCG-metaanalysis)
## Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

<table>
<thead>
<tr>
<th>Therapy and Prevention</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td>1b B ++</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>1b A +</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td>1b B ++</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>1b A +</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
<td>5 D -</td>
</tr>
<tr>
<td><strong>DXA-scan at baseline in pts with AI or premature menopause</strong></td>
<td>5 D +</td>
</tr>
<tr>
<td><strong>Repeat DXA-scan based on risk</strong></td>
<td>5 D +</td>
</tr>
</tbody>
</table>
Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

- Physical activity  
- Avoiding immobilisation  
- Calcium (1000–1500 mg/d)**  
- Vitamine D3 suppl. (800–2000 U/d)  
- Cessation of smoking, reduction of alcohol  
- Avoiding BMI < 20 mg/m²  
- Drugs approved for the treatment of osteoporosis in adults (see next slide)

**if nutritional supply is insufficient, (in combination with Vit D3 only)
### Medical Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate 70 mg po/w*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Denosumab 60 mg sc/6m*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate 150 mg po/m*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate 3 mg iv/3m</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84) 100 µg sc/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Raloxifene 60 mg po/d (improves spine only)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Risedronate 35 mg po/w*</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Strontium ranelate 2 g po/d **</td>
<td>1b B +</td>
</tr>
<tr>
<td>Teriparatide (1-34) 20 µg sc/d</td>
<td>1b B +</td>
</tr>
<tr>
<td>Zoledronate 5 mg iv/12 m*</td>
<td>1b B ++</td>
</tr>
</tbody>
</table>

* 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
**Tabelle 4.2:** Indikation für eine medikamentöse Osteoporosetherapie nach Risikoprofil in Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.\(^1\)

<table>
<thead>
<tr>
<th>Lebensalter in Jahren</th>
<th>T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score &gt; -2,0 nicht sicher belegt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2,0 bis -2,5</td>
</tr>
<tr>
<td>Frau 50-60</td>
<td>Nein</td>
</tr>
<tr>
<td>60-65</td>
<td>60-70</td>
</tr>
<tr>
<td>65-70</td>
<td>70-75</td>
</tr>
<tr>
<td>70-75</td>
<td>80-85</td>
</tr>
<tr>
<td>&gt;75</td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

\(^1\) 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, wenn:**
- Glukokortikoide oral \(\geq 2,5\) mg und \(< 7,5\) mg Prednisolonäquivalent tgl. (außer bei rheumatoide Arthritis +0,5)
- Diabetes mellitus Typ 1
- \(\geq 3\) niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)
Osteo-oncology and Bone Health (2/20)

No further information

No references
Bisphosphonates in Metastatic Breast Cancer (3/20)

No further information

References:

Metaanalysen and Reviews (metastatic breast cancer):


Results of Phase III trials (metastatic breast cancer):


**Denosumab in Metastatic Breast Cancer (4/20)**

No further information

**References:**

Denosumab - Therapy of bone metastases and skeletal related complications:


**Statement: Progression under bisphosphonates**

CALBG 70604: Longer-Interval vs Standard Dosing of Zoledronic Acid (5/20)

No further information

No references
Bone modifying Agents for the Therapy of Bone Metastases (6/20)

No further information

References:

2. Hortobagyi GN et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9500).
5. Templeton AJ et al. Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks: A noninferiority phase III trial (SAKK 96/12, REDUSE). J Clin Oncol 32:5s, 2014 (suppl; abstr TPS5095)
Skeletal Metastasis Treatment with Radionuclids (7/20)

No further information

References:

Reviews / Overview


$^{186}$Rhenium ($^{186}$Re-HEDP)


93Sm (153Sm-EDTMP)


89Sr (89Sr-Chlorid)


223Ra-dichloride:

Metastatic Bone Disease of the Spine – Indication for surgery (8/20)

Further information:

References:

Bone Metastases Acute Spinal Cord Compression / Paraplegia (9/20)

Further information:

References:


Surgery for Bone Metastases Technical Aspects (10/20)

Further information:

References:

Metastatic Bone Disease: Radiotherapy (11/20)

Further information:

References:

Metastatic Bone Disease Recurrent Bone Pain after RT (12/20)

Further information:

References:

Recurrent bone pain in pre-irradiated parts of the skeleton

Magnetic resonance-guided focused ultrasound


Cryoablation / Radiofrequency ablation

Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (13/20)

Further information:

References

Bisphosphonates

Denosumab

Recommendations for Prevention of Osteonecrosis of the Jaw (ONJ) (14/20)

Further information

References:

Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage (15/20)

No further information

References:

Clodronate:


**Adjuvant Aminobisphosphonates**


Dosage of Adjuvant Bisphosphonates for Improvement of Survival (16/20)

No further information

References:

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/20)

No further information

References:

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (18/20)

No further information

References:

Medical Treatment of Osteoporosis (19/20)

No further information

References:

1. German guidelines for the treatment of osteoporosis by the DVO:

Raloxifene


Strontium renalate

Guidelines of the DVO (20/20)

No further information

References:

1. German guidelines for the treatment of osteoporosis by the DVO:
Specific Sites of Metastases
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
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

- Histological / cytological verification
- Systemic treatment preferred
- Consider surgery only in case of good response to palliative treatment
- Metastases surgery is an option for pts in good conditions with late onset oligometastases
- Local treatment in the case of pain, exulceration, persistence after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression
- Systemic treatment after surgery

* See chapters with systemic treatment recommendations
Local Therapy in Primary Metastatic Disease

- Surgery (R0) of the primary tumor
  - In case of bone metastases only
  - In case of visceral metastases
- Axillary surgery for cN1
- Sentinel if cN0
- Radiotherapy of the primary tumor
  - Alone (without surgery)
  - After local surgical treatment with BCS or mastectomy (acc. adjuvant indication)

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\(^\) 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 +
Liver Metastasis
Local Therapy

- **Resection of liver metastasis (R0)**
  - 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**

- **Regional radiotherapy**
  - [SIRT, stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT), radiochemoembolization, other modalities]

- **Thermoablation**
  - (RFA, LITT, cryotherapy)
Pulmonary Metastases
Local Therapy

- Before any surgery: staging and biopsy (CT-guided FNA / CNB or transbronchial FNA)
- Resection of pulmonary metastases by VATS or conventional resection
  - In case of multilocular metastatic disease
  - In case of single / few unilateral metastases with curative intent
- Thermoablation (CT-guided RFA, LITT)
- Regional radiotherapy
  (e.g. stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT))

*VATS = video-assisted thoracic surgery
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

- If expected life time is short, less invasive procedures should be considered
- VATS and Talcum-pleurodesis*
- Chemical pleurodesis*
  - Talcum powder
  - Bleomycin, Doxycycline, Mitoxantrone
  - Povidone-iodine (20 ml of 10% solution)
- Continuous pleural drainage
- Systemic treatment after pleurodesis
- Local antibody therapy (i.e. Catumaxomab)
- Serial thoracocentesis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of Evidence</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>If expected life time is short</td>
<td>4</td>
<td>C++</td>
<td>++</td>
</tr>
<tr>
<td>VATS and Talcum-pleurodesis*</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Chemical pleurodesis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talcum powder</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Bleomycin, Doxycycline, Mitoxantrone</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Povidone-iodine (20 ml of 10% solution)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Continuous pleural drainage</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Systemic treatment after pleurodesis</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Local antibody therapy (i.e. Catumaxomab)</td>
<td>3b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Serial thoracocentesis</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Adequate pain-relief

VATS: video-assisted thoracoscopic surgery
## Malignant Ascites

### Local Therapy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puncture, drainage in symptomatic patients</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>3b</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Local chemotherapy</td>
<td>3b</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Local antibody therapy (i.e. Catumaxomab)</td>
<td>3b</td>
<td>D</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Symptomatic pericardial effusion:

- Drainage, fenestration: 3b B ++
- Combination with optimized systemic therapy: 4 C ++
- VATS (video-assisted thoracic surgery): 4 C +
- Ultrasound guided puncture and instillation of cytotoxic compounds
  - Bleomycin, cisplatinum, mitomycin C, mitoxantrone etc.: 4 C +/-
  - Bevacizumab: 4 C +/-
Bone Marrow Infiltration Associated with Pancytopenia

- Weekly chemotherapy with*:
  - Epirubicin, Doxorubicin, Paclitaxel
  - Capecitabine
- HER2 pos.:
  add anti-HER2 -treatment

* Consider pre-treatment

Oxford / AGO LoE / GR

- 4 D ++
- 4 D ++
- 5 D ++
## Soft Tissue Metastasis

### Local Therapy

<table>
<thead>
<tr>
<th>Soft Tissue Metastasis</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin, muscular, nodal</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Paresis, spinal cord compression</td>
<td>2b C ++</td>
</tr>
<tr>
<td>Plexus infiltration</td>
<td>3b C ++</td>
</tr>
</tbody>
</table>

- **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
  - Paresis, spinal cord compression
  - Plexus infiltration
Specific Sites of Metastases (2/13)

No further information

References

Sources for this chapter of the AGO-Guideline

Pubmed 1.1.2016 bis 31.1.2017


Specific Sites Of Metastases (3/13)

No further information

No references
General Aspects of Metastases Surgery or Ablation (4/13)

No further information

References:

17. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013
Local Therapy in Primary Metastatic Disease (5/13)

Further information and references:

Statements:
Local surgical treatment (R0) of primary tumor (1b B +/-)

9. Soran A et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) SABCS [S2-03], 2013
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 +)
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


Statement: Regional chemotherapy (3b C +/-)


Statement: Regional radiotherapy (4 C +/-)

Statement: Thermoablation (3b C +/-)

**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 +/-)


Statement: Thermoablation (CT-guided RFA, LITT) (3b C +/-)


Statement: Regional radiotherapy (4 C +/-)

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,
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 ++)


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 +/-)


Statement: Continous pleural drainage (2a B +)

Statement: Systemic treatment after pleurodesis (3b C +/−)

Statement: Local antibody therapy (i.e. Catumaxomab) (3b C −)

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:

Malignant Pericardial Effusion - Local Therapy (11/13)

Further information:

Malignant pericardial effusion and cardiac tamponade remains a rarity, which are known complications of many advanced malignancies such as breast cancer, lung cancer, lymphomas and leukemias. In general overall survival is low, due to other metastatic localizations. The standard treatment of malignant effusion and cardiac tamponade has not yet been defined. Physicians should consider the status and the prognosis of each case.

In symptomatic patients drainage and fenestration are the treatment options of choice. VATS is an alternative treatment option. In individual cases US-guided puncture with instillation of mitoxantrone is possible.

References:

**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:*


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:

CNS Metastases in Breast Cancer
CNS  Metastases in Breast Cancer

 ➤ Versions 2003–2016:

 Bischoff / Diel / Friedrich / Gerber / Huober / Loibl / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

 ➤ Version 2017:

 Fehm / Witzel

 In collaboration with:

 P. Feyer und D. Rades (DEGRO)
CNS Metastases in Breast Cancer – Incidence

- Breast cancer is the 2nd most common cause of CNS metastases
- At autopsy:
  - Parenchymal CNS metastases: ~30–40%
  - Leptomeningeal CNS metastases: ~5–16%
- Increasing incidence (10% ⇒ 40%)
- Increasing incidence due to
  - More effective treatment of extracerebral sites with improved prognosis
  - Increasing use of MRI in diagnostic evaluation
- Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de)
CNS Metastases in Breast Cancer (BC) Risk Factors

- **Primary Tumor:**
  - Negative estrogen receptor status (basal-like cell type / triple-negative)
  - High grading, high Ki-67 index
  - HER2 and/or EGFR (HER1) overexpression
  - 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

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
<td>n/a</td>
<td>____</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
<td>LumA</td>
<td>HER2</td>
<td>LumB</td>
<td>____</td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>____</td>
</tr>
</tbody>
</table>

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
# Rades Score* - Worksheet to Estimate Survival from Brain Metastases (BM) by plus chemotherapy Diagnosis

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>6-months survival rate(%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 60 years</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>≥ 61 years</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td><strong>Karnofsky-Index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>≥ 70</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td><strong>Extracranial metastases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td>yes</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td><strong>Interval from first diagnosis to WBRT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 8 months</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 8 months</td>
<td>36</td>
<td>4</td>
</tr>
</tbody>
</table>

**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
Single / Solitary Brain Metastasis

Local therapy alone: SRS (≤ 4 cm) o. FSRT o. Resection
WBRT + Boost (SRS, FSRT) o. Resection + WBRT
Resection + Irradiation of the tumor bed (without WBRT)
WBRT alone*
Hippocampal-sparing

- 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 tumor bed has to be irradiated (either local RT or boost in case of WBRT). In general there is no advantage of surgical resection over RT.

* Patients with reduced general conditions and limited life expectancy

SRS = stereotactic radiosurgery (single session)
FSRT = fractionated stereotactic RT
WBRT = whole brain radiotherapy
2-3 (2-4) Brain Metastases (Oligo-)

Local therapy alone: SRS (≤ 4 cm) or FSRT
WBRT + Boost (SRS, FSRT)

WBRT alone *
Hippocampal-sparing

- 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
NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases

Study design:
Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.

Conclusion:
Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

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

<table>
<thead>
<tr>
<th></th>
<th>after surgical resection (n=160)</th>
<th>after radiosurgery (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBRT</td>
<td>observation</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>27%</td>
<td>59% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>19%</td>
<td>31% (p=0.040)</td>
</tr>
<tr>
<td>New lesions</td>
<td>23%</td>
<td>42% (p=0.008)</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>48% (p=0.023)</td>
</tr>
</tbody>
</table>

- 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.

Kocher M. J Clin Oncol 2011, 29:134-141
Possible Factors for Decision Making
Neurosurgery versus Stereotactic Radiosurgery

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
## Multiple Brain Metastases >3 (4) Lesions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>WBRT (supportive steroids</em>)</em>*</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>SRS/FSRT</strong></td>
<td>4 C +/-</td>
</tr>
<tr>
<td><strong>Hippocampal-sparing radiotherapy</strong></td>
<td>2b C +/-</td>
</tr>
<tr>
<td><strong>Radiochemotherapy</strong> for cerebral disease control</td>
<td>3b C -</td>
</tr>
<tr>
<td><strong>Chemotherapy alone</strong></td>
<td>3a D +/-</td>
</tr>
<tr>
<td><strong>Corticosteroids alone</strong>*</td>
<td>3a B +/-</td>
</tr>
<tr>
<td><strong>Re-irradiation if recurrence</strong></td>
<td>4 C +/-</td>
</tr>
</tbody>
</table>

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
### Systemic and Symptomatic Therapy of Brain Metastases*

* In addition to local therapy

<table>
<thead>
<tr>
<th>Suggestion</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuation of the actual systemic therapy if first diagnosis of brain metastases and stable extracranial disease</td>
<td>2c C +</td>
</tr>
<tr>
<td>Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Chemotherapy alone as primary treatment</td>
<td>3 D -</td>
</tr>
<tr>
<td>Anticonvulsants only if symptoms of seizures</td>
<td>3 C +</td>
</tr>
<tr>
<td>Glucocorticoids only when symptoms and / or mass effect</td>
<td>3 C ++</td>
</tr>
</tbody>
</table>
Leptomeningeal Carcinomatosis
Local Therapy

**Intrathecal or ventricular therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Liposomal cytarabine 50 mg, q 2w</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Thiothepa</td>
<td>3b C +</td>
</tr>
<tr>
<td>Steroids</td>
<td>4 D +/-</td>
</tr>
<tr>
<td>Trastuzumab (HER2 pos. disease)</td>
<td>4 C +/-</td>
</tr>
</tbody>
</table>

**Radiotherapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal (bulky disease)</td>
<td>4 D +</td>
</tr>
<tr>
<td>WBRT</td>
<td>4 D +</td>
</tr>
<tr>
<td>Neuroaxis (disseminated spinal lesions)</td>
<td>4 D +/-</td>
</tr>
</tbody>
</table>

Due to bad prognosis consider best supportive care, especially in patients with poor performance status.
No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/14)

No further information

References:

Further information:

HER2-positive and triple negative patients are at increased risk for the development of CNS metastases. Nevertheless, no evidence for screening exists. Better systemic control (especially in HER2-positive patients) is supposed to improve survival, thereby leading to an “unmasking” of cerebral metastases. This is attributed to insufficient control of cerebral tumor spread by current treatment strategies as well as to a higher CNS-tropism of HER2-positive and triple-negative tumor cells (see references).

References:

References risk factors (see also references slide CNS incidence):


Brain metastases (BM) are more likely to be estrogen receptor negative, and overexpress HER2 or EGFR.


References: 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 (5/14)

No further information

References:

References for Breast-GPA:


Further References: Prognostic Factors for Survival:


Rades OS-Score (6/14)

No further information

Reference:


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.

References:


Brain Metastases 2-3 (2-4) lesions (8/14)

No further information

References:

See references Slide 7
NCCTG N0574 (Alliance): (9/14)

No further information

Reference:

EORTC 22952-26001 Study (10/14)

No further information

Reference:

Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (11/14)

*No further information*

*No references*
Multiple Brain Metastases (12/14)

No further information

References:


Radiochemotherapy


Re-Bestrahlung bei Rezidiv


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 3 or 4 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.

References:


Chemotherapy


Anticonvulsants


Steroids

Leptomeningeal Carcinomatosis Local Therapy (14/14)

No further information

References:

Trastuzumab intrathecal


MTX high dose

Complementary Therapy

Survivorship
Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

- **Versionen 2002–2016:**
  Albert / Bauerfeind / Blohmer / Fersis / Friedrich / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

- **Version 2017:**
  Gerber / Lück
„Alternative“ Therapies

„Integrative Oncology“

CAM
Complementary + alternative medicine

Complementary
In addition to scientifically based medicine

Alternative
Instead of scientifically based medicine

„Unconventional methods“

UCT
Unconventional Thx

Unconventional
Unproven outsider methods

Problems of available studies: selection bias, small case numbers, short follow-up, contrary results etc.
General Considerations

Alternative methods (CAM) instead of surgical treatment
Alternative methods (CAM) instead of systemic treatment
While on anti-cancer treatment: beware of drug interactions
## Complementary Therapy
### Pre- and Postoperative

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Hypnosis (reduces anxiety, pain, nausea)</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>➢ Acupuncture (pain relief, anxiety)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>➢ Acupuncture (nausea, vomiting)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td><strong>Postoperative:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Massage therapy (pain relief)</td>
<td>2b</td>
<td>C</td>
</tr>
<tr>
<td>➢ Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage)</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>➢ Prophylactic lymph drainage</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

*Oxford AGO LoE / GR*
Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

- **Mistletoe (Viscum album)**
  in order to reduce side effects

- **Thymic peptides**
  lowered risk of severe infections

- **Ginseng**
  in order to reduce cancer related fatigue; note: inhibits cytochrome P enzymes e.g. CYP 3A4

- **Ganoderma Lucidum**
  may improve fatigue, note: inhibits cytochrome P enzymes e.g. CYP 3A4)

- **L-Carnitine**
  - given for prevention of toxicity, increased chemotherapy induced peripheral neuropathy
  - Improvement of cancer related fatigue

- **Curcumin**
  as an adjunct to reduce radio dermatitis

- **Ginger**
  for chemotherapy induced nausea & vomiting

---

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level</th>
<th>Rating</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mistletoe</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Thymic peptides</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ginseng</td>
<td>2b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Ganoderma Lucidum</td>
<td>2b</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>1b</td>
<td>B</td>
<td>--</td>
</tr>
<tr>
<td>Curcumin</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Ginger</td>
<td>1b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Complementary Treatment
Impact on Toxicity II

- Antioxidant supplements  
- High dose vitamine C  
- Vitamine E  
- Selenium for alleviating side effects of therapy  
- Co-Enzyme Q 10 (fatigue, QoL)  
- Proteolytic enzymes in order to reduce chemotherapy-induced toxicity  
- Chinese herbal medicine improves wound healing  
- Oxygen and ozone therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / LoE</th>
<th>AGO / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant supplements</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>High dose vitamine C</td>
<td>1b</td>
<td>C</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>2b</td>
<td>D</td>
</tr>
<tr>
<td>Selenium for alleviating side effects of therapy</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Co-Enzyme Q 10 (fatigue, QoL)</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Proteolytic enzymes in order to reduce chemotherapy-induced toxicity</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>Chinese herbal medicine improves wound healing</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Oxygen and ozone therapy</td>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>

*inf: i.v.-infusion (in Germany not approved)
Additional Complementary Therapy
Side Effects Related to Cancer Treatments
e.g. Chemotherapy

- Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients
- Homoeopathic medicines for adverse effects of cancer treatments
  - 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
- Acupuncture in order to improve on
  - Chemotherapy-induced >=nausea and vomiting
  - Cognitive dysfunction
  - Fatigue
  - Pain
  - Leucopenia (Moxibustion)
  - Hot flashes
  - Treatment of chemotherapy induced polyneuropathy

Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LoE</th>
<th>Grade</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese medicinal herbs to treat the side effects of chemotherapy in breast cancer patients</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Homoeopathic medicines for adverse effects of cancer treatments</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>Topical calendula (&gt;= 20% Calendula amount) for prophylaxis of acute dermatitis during radiotherapy</td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Traumeel S® mouthwash to treat chemotherapy-induced stomatitis</td>
<td></td>
<td></td>
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<tr>
<td>Topical Silymarin for prophylaxis of acute dermatitis during radiotherapy</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Acupuncture in order to improve on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy-induced &gt;=nausea and vomiting</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Pain</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Leucopenia (Moxibustion)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Treatment of chemotherapy induced polyneuropathy</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>
Complementary Treatment
Mind-Body Medicine I

MBSR (Mindfulness-Based Stress Reduction)
Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes)

Physical exercise / sport
min. 150 min. moderate endurance training per week in combination with work out exercises (2x per week) improve quality of life, cardio-respirat. fitness, physical performance and fatigue, no higher risk of lymphedema

Oxford / AGO
LoE / GR

1a  A  +

1a  A  ++
Complementary Treatment
Mind-Body Medicine II

- **Yoga**
  - Improves sleep, quality of life, stress, anxiety, depression, fatigue

- **Qi Gong**
  - May improve quality of life, fatigue, mood

- **Tai Chi**
  - Improves quality of life, physical performance

- **Hypnosis (in combination with cognitive training)**
  - Improves fatigue and muscle weakness under radiation therapy, also reduces distress

---

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A +</td>
<td></td>
</tr>
<tr>
<td>2a B +/-</td>
<td></td>
</tr>
<tr>
<td>2a B +/-</td>
<td></td>
</tr>
<tr>
<td>1b A +</td>
<td></td>
</tr>
</tbody>
</table>
### Modifiable Lifestyle Factors

**Prevention of Recurrence/ Improvement of Overall Survival I**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Alcohol consumption (&gt;6 g/day)</strong></td>
<td>2b</td>
<td>A</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Modifiable Lifestyle Factors
Nutrition after Breast Cancer Diagnosis
Prevention of Recurrence / Improvement of Overall Survival II

- Adherence to normal BMI/weight loss if overweight, irrespective of HR-status
  - LoE: 1a, GR: A++, Evidence level: ++

- Low fat diet
  - Dietary counseling recommended
  - LoE: 1a, GR: A+, Evidence level: +

- Avoid high-fat dairy food
  - LoE: 2b, GR: C+, Evidence level: +

- Flaxseed / increased fibre intake
  - LoE: 2a, GR: B+, Evidence level: +

- Adherence to general nutrition guidelines (e.g. DGE, WCRF)
  - LoE: 2a, GR: B++, Evidence level: ++

- Dietary extremes
  - LoE: 1b, GR: B-, Evidence level: -
Complementary Treatment
Prevention of Recurrence / Improvement of Overall Survival III
Dietary Supplements – Herbal Therapies

Post treatment vitamin/antioxidant supplements doesn't appear to be associated with increased risk of recurrence (beware of drug/treatment interactions)
Smokers on antioxidant supplements are at higher risk for lung cancer

For Prevention of BC Recurrence:
- Antioxidants
- Orthomolecular substances (Selenium, Zinc...)
- Vitamine supplementation in pts on a balanced diet (esp. Vit C, E, D)
- Artificial carotenoids appear to be associated with worse outcome
- Proteolytic enzymes (Papain, Trypsin, Chymotrypsin)
- Soy-food (natural source of phytoestrogens)
- Concentrates containing ≥ 100 mg isoflavones
- Black Cohosh (Cimicifuga racemosa)
- Mistletoe (Viscum album)
- Thymic peptides (impact on OS)
- Oxygen- and ozone therapy
- Antioxidant supplements (after completion of radiotherapy)
- Laetrile
- Methadon
- Cancer bush (Sutherlandia frutescens), Devil's claw (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis), Bambara groundnut (Vignea subterranea)

<table>
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<th>Complementary Treatment</th>
<th>Oxford</th>
<th>AGO</th>
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<tbody>
<tr>
<td>Post treatment vitamin/antioxidant supplements doesn't appear to be associated with increased risk of recurrence (beware of drug/treatment interactions)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Smokers on antioxidant supplements are at higher risk for lung cancer</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Orthomolecular substances (Selenium, Zinc...)</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Vitamine supplementation in pts on a balanced diet (esp. Vit C, E, D)</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Artificial carotenoids appear to be associated with worse outcome</td>
<td>2b</td>
<td>B -</td>
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<tr>
<td>Proteolytic enzymes (Papain, Trypsin, Chymotrypsin)</td>
<td>3b</td>
<td>B -</td>
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<tr>
<td>Soy-food (natural source of phytoestrogens)</td>
<td>2a</td>
<td>B +/-</td>
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<tr>
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<td>2a</td>
<td>B -</td>
</tr>
<tr>
<td>Black Cohosh (Cimicifuga racemosa)</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Mistletoe (Viscum album)</td>
<td>1b</td>
<td>C</td>
</tr>
<tr>
<td>Thymic peptides (impact on OS)</td>
<td>2a</td>
<td>B -</td>
</tr>
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<td>2b</td>
<td>B +/-</td>
</tr>
<tr>
<td>Laetrile</td>
<td>1c</td>
<td>D -</td>
</tr>
<tr>
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<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Cancer bush (Sutherlandia frutescens), Devil's claw (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis), Bambara groundnut (Vignea subterranea)</td>
<td>5</td>
<td>D -</td>
</tr>
</tbody>
</table>
Complementary Treatment
Cancer Pain Reduction

- Acupuncture for cancer pain in adults
- Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults
- Cave: No delay in diagnostic process

Oxford / AGO LoE / GR

1a B +/-
2b D +/-
Further information:

Screened Data Sources:
- Pubmed: 2012 - 01/2017
- Cochrane library: summary Jan. 2017:

No references
Further information:

The term „alternative therapies“ has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.

- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

No references
No further information

References:


Complementary Therapy Pre- and Postoperative (5/14)

No further information

References:

Hypnosis


Acupuncture and Postoperative Nausea and Vomiting


Massage Therapy

Postoperative exercise

Prophylactic lymph drainage


**Complementary Treatment. Treatment phase. Impact on Toxicity I (6/14)**

*No further information*

**References:**

**General:**


**Mistletoe:**


Thymus:


Ginseng, Ganoderm lucidum:


L-Carnitine:


Curcumin:

Complementary Treatment. Treatment phase. Impact on Toxicity II (7/14)

No further information

References:

General:


Antioxidant supplements

Vitamin C


Selen


Coenzym Q10

Proteolytic enzymes and toxicity of chemotherapy:


Bromelain


Chinese herbal medicine and wound healing

Additional Complementary Therapy Side Effects Related to Cancer Treatments - e.g. Chemotherapy
(8/14)

No further information

References:

Chinese medicinal herbs


Homeopathic medicines for adverse effects of cancer treatments


Topical use of Silymarin


Acupuncture


Chemotherapy-induced Nausea and Vomiting

Cognitive dysfunction


Fatigue


Pain


Leucopenia


Chemotherapy induced peripheral neuropathy

Complementary Therapies - Mind-Body-Medicine I (9/14)

No further information

References:

Mind-Body Medicine (MBM)


MBSR


Physical exercise


Statement on quality of life


Cardio respiratory Fitness / Physical Functioning


Fatigue


Complementary Therapies - Mind-Body-Medicine II (10/14)

No further information

References:

General


Yoga


**Qigong**


Tai Chi


Hypnosis


No further information

References:

Physical exercise


**Improvements in DFS and OS, prevention of recurrence**


Smoking


Alcohol


**Modifiable Lifestyle Factors – Nutrition after Breast Cancer Diagnosis – Prevention of Recurrence II / Improvement of Overall Survival II (12/14)**

*No further information*

**References:**

**Adherence to normal body weight/BMI:**


Avoidance of high fat dairy products:

Lignans/ flaxseed:


Adherence to general nutrition – guidelines:

Complementary Treatment - Prevention of Recurrence / Improvement of Overall Survival III Dietary Supplements – Herbal Therapies (13/14)

No further information

References:

General:


Post treatment vitamin and/or antioxidant supplements:


Soy as normal part of the diet/soy concentrates:


Black cohosh:


Laetrile treatment for cancer:


St John’s Wort:


Red clover:


Dong Quai:


Ginseng root:


Bromelain+Papain+Selen+Lektin bei AI-induced athralgia

Complementary Treatment: Cancer Pain Reduction (14/14)

No further information

References:

Acupuncture:

Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults:


Gynaecological Issues in Breast Cancer Patients
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

- **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**
  - **4** D +/-
  - **4** C -
    - **Course:** 4 weeks daily 1x1, further 8 weeks: 3 x 1 per week
# Further Medical Approaches to Reduce Menopausal Symptoms I

**Medical approaches:**

- Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI): reduce hot flashes in BC patients
  - 1\(^{\text{st}}\) choice: venlafaxine
  - 2\(^{\text{nd}}\) choice: desvenlafaxine
  - 3\(^{\text{rd}}\) choice: sertraline, escitalopram

- Gabapentin (patients using TAM)

- Pregabalin

- Clonidine (patients using TAM)

- MPA (i.m. 500 mg single shot)
  (most potent, but endocrine agent!)

- Vitamine E

- Melatonin (improvement in sleep quality)

---

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors and serotonin-(noradrenalin) reuptake inhibitors (SSRI-SNRI)</td>
<td>1(^{\text{a}}) A +</td>
<td></td>
</tr>
<tr>
<td>1(^{\text{st}}) choice: venlafaxine</td>
<td>1b A +/-</td>
<td></td>
</tr>
<tr>
<td>2(^{\text{nd}}) choice: desvenlafaxine</td>
<td>1b A +/-</td>
<td></td>
</tr>
<tr>
<td>3(^{\text{rd}}) choice: sertraline, escitalopram</td>
<td>1b A +/-</td>
<td></td>
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<tr>
<td>Gabapentin (patients using TAM)</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>1b A +/-</td>
<td></td>
</tr>
<tr>
<td>Clonidine (patients using TAM)</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>MPA (i.m. 500 mg single shot)</td>
<td>1b A +/-</td>
<td></td>
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<tr>
<td>(most potent, but endocrine agent!)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamine E</td>
<td>1b A -</td>
<td></td>
</tr>
<tr>
<td>Melatonin (improvement in sleep quality)</td>
<td>2b C +</td>
<td></td>
</tr>
</tbody>
</table>
CAM* - Approaches to Reduce Menopausal Symptoms II

* Complementary and Alternative Medicine

While anti-cancer treatment: Beware of drug interactions!

- **Soy-derived phytoestrogens – isoflavonoids**
  - Hot flush
  - Sleep disturbance
  - Topical vaginal application
  - LoE: 1b, AGO: B, Inter: -

- **Red Clover isoflavonoids**
  - Hot flush, sleep disturbance
  - (might stimulate BC especially in endocrine responsive disease)
  - LoE: 1b, AGO: B, Inter: +/-

- **Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)**
  - (reduces relapses, no effect on hot flashes)
  - LoE: 2b, AGO: B, Inter: +/-

- **Black Cohosh for hot flushes**
  - LoE: 1b, AGO: B, Inter: -

- **Black cohosh + St. John’s Worth**
  - LoE: 1b, AGO: B, Inter: +/-

- **St. John’s Wort (in combination-therapy)**
  - (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)
  - LoE: 1b, AGO: B, Inter: --

- **Ginseng root (Panax ginseng or P. quinquefolius)**
  - LoE: 1b, AGO: B, Inter: -

- **Bromelain + Papain + Selen + Lektin (for, AI induced joint symptoms)**
  - LoE: 3b, AGO: B, Inter: +
General Approaches to Reduce Menopausal Symptoms III Integrative Oncology Aspects

General approaches:

- Physical exercise
  - Oxford / AGO LoE / GR: 1b B ++

- Mind body-medicine (yoga, hypnosis, education, counselling)
  - Oxford / AGO LoE / GR: 1b B +

- Cognitive behavioral therapy (CBT)
  - Oxford / AGO LoE / GR: 1b B ++

- Acupuncture
  - Aromatase-inhibitor treatment induced arthralgia
    - Oxford / AGO LoE / GR: 2b B +
  - Hot flashes
    - Oxford / AGO LoE / GR: 1b B +
  - Depression
    - Oxford / AGO LoE / GR: 2b B +/-
  - Anxiety, Sleep
    - Oxford / AGO LoE / GR: 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)

- **For ovarian function protection**
  CT + GnRHa
  (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status)

- **Fertility preservation counselling**

- **Fertility preservation using assisted reproduction therapy (ART)**
  (further information www.fertiprotect.de)

Oxford / AGO LoE / GR

1a B +

4 C ++

4 C +
# Ovarian Function Preservation – Comparison of Randomized Trials

<table>
<thead>
<tr>
<th></th>
<th>ZORO</th>
<th>PROMISE</th>
<th>Munster et al. - US</th>
<th>POEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient number</strong></td>
<td>60 (60 HR-)</td>
<td>281 (50 HR-)</td>
<td>49 (13 HR-) of 124</td>
<td>218 (218 HR-)</td>
</tr>
<tr>
<td><strong>Age median</strong></td>
<td>38 years</td>
<td>39 years</td>
<td>39 years</td>
<td>Premenop. &lt; 50 years</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>goserelin</td>
<td>triptorelin</td>
<td>triptorelin</td>
<td>goserelin</td>
</tr>
<tr>
<td><strong>Start of treatment</strong></td>
<td>&gt;2 weeks prior to cht</td>
<td>&gt;1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
<td>&gt; 1 week prior to cht</td>
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<tr>
<td><strong>Primary Endpoint</strong></td>
<td>menstruation at month 6 after chemotherapy</td>
<td>rate of early menopause at month 12 after chemotherapy</td>
<td>menstruation rate within 2 years after cht</td>
<td>Ovarian failure at 2 yrs after cht</td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td>to detect 30% absolute increase of menstruation rate</td>
<td>to detect at least 20% absolute reduction in early menopause</td>
<td>to detect 20% difference in amenorrhea rate - from 10% to 30%</td>
<td></td>
</tr>
<tr>
<td><strong>Multivar. analysis</strong></td>
<td>age as only independent predictive factor</td>
<td>treatment as only independent predictive factor</td>
<td>n.d.</td>
<td>Treatment as only Independent predictive factor</td>
</tr>
<tr>
<td><strong>Resumption of menses at month 12 in HR- cohort</strong></td>
<td>83% with LHRH vs. 80% w/o</td>
<td>93% with LHRHa vs. 74% w/o</td>
<td>74% with LHRH vs. 68% w/o</td>
<td>78% with LHRH vs. 75% w/o; at 2 years; 22% with LHRH vs. 8%</td>
</tr>
<tr>
<td><strong>Median time to restoration of menses (months)</strong></td>
<td>6.1 with LHRHa vs. 6.8 w/o; p=0.30</td>
<td>not reached with LHRH vs. 6.7 w/o; p=0.07</td>
<td>5.8 with LHRH vs. 5.0 w/o; p=0.58</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Cyclophosph. dose</strong></td>
<td>4600 vs. 4700mg</td>
<td>4080 vs. 4008 mg</td>
<td>n.r.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Odds Ratio</th>
<th>95%CI</th>
<th>Treated Events</th>
<th>Controls Events</th>
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<tbody>
<tr>
<td>Li M (2008)</td>
<td>0.31</td>
<td>0.11-0.89</td>
<td>8/31</td>
<td>17/32</td>
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<tr>
<td>Badaway (2009)</td>
<td>0.06</td>
<td>0.02-0.20</td>
<td>4/39</td>
<td>26/39</td>
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<td>Sverrisdottir 1 (2009)</td>
<td>0.19</td>
<td>0.04-1.06</td>
<td>14/22</td>
<td>18/20</td>
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<tr>
<td>Sverrisdottr 2 (2009)</td>
<td>2.03</td>
<td>0.31-13.27</td>
<td>27/29</td>
<td>20/23</td>
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<tr>
<td>Del Mastro (2011)</td>
<td>0.27</td>
<td>0.14-0.54</td>
<td>13/148</td>
<td>35/133</td>
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<td>Gerber (2011)</td>
<td>0.56</td>
<td>0.19-1.62</td>
<td>9/30</td>
<td>13/30</td>
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<td>Sun (2011)</td>
<td>0.38</td>
<td>0.06-2.30</td>
<td>3/11</td>
<td>5/10</td>
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<td>Munster (2012)</td>
<td>1.09</td>
<td>0.22-5.52</td>
<td>4/26</td>
<td>3/21</td>
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<td>Elgindy 1 (2013)</td>
<td>0.76</td>
<td>0.18-3.25</td>
<td>4/25</td>
<td>5/25</td>
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<td>Elgindy 2 (2013)</td>
<td>1.0</td>
<td>0.25-4.00</td>
<td>5/25</td>
<td>5/25</td>
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<td>Song (2013)</td>
<td>0.50</td>
<td>0.25-1.03</td>
<td>15/89</td>
<td>27/94</td>
</tr>
<tr>
<td>Karimi-zarchi (2014)</td>
<td>0.05</td>
<td>0.01-0.29</td>
<td>2/21</td>
<td>14/21</td>
</tr>
<tr>
<td>Li JW (2014)</td>
<td>0.44</td>
<td>0.04-4.35</td>
<td>1/54</td>
<td>3/73</td>
</tr>
<tr>
<td>Moore (2015)</td>
<td>0.30</td>
<td>0.10-0.87</td>
<td>5/66</td>
<td>15/69</td>
</tr>
<tr>
<td>Summary: Fixed effect</td>
<td>0.34</td>
<td>0.25-0.46</td>
<td>114/616</td>
<td>206/615</td>
</tr>
<tr>
<td>Summary: Random effect</td>
<td>0.36</td>
<td>0.23-0.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure


The use of LHRHa was associated with a significant reduced risk of premature 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-RHα for Prevention of Premature Ovarian Failure


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

Tests for fertility assessment

- Anti-Müllerian Factor
- Antral follicle count

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

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Details</th>
</tr>
</thead>
</table>
| FSH (follicle stimulating hormone)  | • 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.
### Contraceptive Options for Women after Diagnosis of Breast Cancer

<table>
<thead>
<tr>
<th>Option</th>
<th>LoE</th>
<th>Cochrane Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier methods</td>
<td>5</td>
<td>D +</td>
</tr>
<tr>
<td>Sterilization (tubal ligation / vasectomy)</td>
<td>5</td>
<td>D +</td>
</tr>
<tr>
<td>Non-hormonal intrauterine devices (IUDs)</td>
<td>3b</td>
<td>D +</td>
</tr>
<tr>
<td>Levonorgestrel-releasing IUDs</td>
<td>2b</td>
<td>C -</td>
</tr>
<tr>
<td>Removal in newly diagnosed patients</td>
<td>4</td>
<td>D +/-</td>
</tr>
<tr>
<td>Timing methods</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Injectable progestin-only contraceptives</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Progestin-only oral contraceptives</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Combined oral contraceptives</td>
<td>5</td>
<td>D -</td>
</tr>
</tbody>
</table>
Emergency Contraception
Options after Diagnosis of Breast Cancer

- Copper intrauterine device (Cu-IUD)

- Levonorgestrel, Ulipristal orally
Sexual Health

- Assessment of sexual dysfunction: 5 C +
- Use of patient-reported questionnaires: 4 C +
- Vaginal dryness: Non-hormonal lubricants / moisturizers: 1b B +
- Psychoeducational support, group therapy, sexual counseling, marital counseling, psychotherapy: 1b B +
Assessment of Sexual Health

- Sexual Complaints Screener (SCS) for women*
  German Translation

Screening-Check-Fragebogen: Overall Sexual Function

1. Are you satisfied with your sexual function?
   yes, no; if no
2. How long have you been dissatisfied with your sexual function?
3. The problem(s) with your sexual function is: (mark one or more):
   1. Problem with little or no interest in sex
   2. Problem with decreased genital sensation (feeling)
   3. Problem with decreased vaginal lubrication (dryness)
   4. Problem reaching orgasm
   5. Problem with pain during sex
   6. Other
4. Which problem is most bothersome? (circle) 1, 2, 3, 4, 5, 6.
5. Would you like to talk about it with your doctor?

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


Tibolone:


**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.

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 symptoms 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.

References:


**SSRI:**


**Venlafaxine**


**Desvenlafaxine**


Paroxetine


Fluoxetine


Citalopram


Gabapentin


**Pregabalin**


**Clonidin**


**(D) MPA (depo-) (Medroxyprogesterone acetate)**

Vitamine E


Melatonin

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.


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-derived 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-derived isoflavonoids**

Topical isoflavones showed beneficial effects on dyspareunia, vaginal dryness and maturation value. Isoflavone vaginal gel was similar to the use of conjugated equine oestrogen cream (0.3 mg/day) was and superior to that of placebo.

**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.


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.


Taken together neither Black cohosh (Cimicifuga racemosa) nor St John’s Wort nor Ginseng root showed a benefit regarding improvement of menopausal symptoms.


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.

Further information:

Physical exercises (PE) and cognitive behavioral therapy (CBT; this is one form of psychotherapy) have positive effects on menopausal symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. The CBT and PE are cost-effective. Prescription 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.

References:


Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/17)

No further information

References:

Ovarian function protection


Fertility preservation counselling


Fertility preservation with assisted reproduction therapy


Further information

This overview compares the different randomised trials comparing fertility preservation with GnRH-analogue without GnRH-analogue.
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.

References:


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 premature 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 premature 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). 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 (I² = 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; I² = 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; I² = 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 premature ovarian failure and seems to increase the pregnancy rate, without an apparent negative consequence on prognosis.“

Reference:

Phase III Studies Evaluating the Role of LH-RHa in the Preservation of Ovarian Function (11/17)

No further information

References:

**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 (antimullerian 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.

**References:**

Assessment of Ovarian Reserve (13/17)

No further information

Reference:

1. Tests recommended to assess ovarian reserved (according to ACOG Committee Opinion No. 618: Ovarian Reserve Testing. Obstetrics & Gynecology 2015 ;125 : 268-273
Contraceptive Options for Women after Diagnosis of Breast Cancer (14/17)

No further information

References:

Emergency Contraception - Options after Diagnosis of Breast Cancer (15/17)

No further information

References:

Sexual Health (16/17)

No further information

References:

1. Runowicz CD1, Leach CR2, Henry NL1, Henry KS1, Mackey HT1, Cowens-Alvarado RL1, Cannady RS1, Pratt-Chapman ML1, Edge SB1, Jacobs LA1, Hurria A1, Marks LB1, LaMonte SJ1, Warner E1, Lyman GH1, Ganz PA1. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2015 Dec 7. pii: JCO.2015.64.3809

Assessment of Sexual Health (17/17)

Further information:

Sexual Complaints Screener (SCS) for women
German Translation

References: