Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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# Oxford Levels of Evidence (LOE)

<table>
<thead>
<tr>
<th>LOE</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
</tr>
</thead>
<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 $\geq 80%$ 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>Full Form</th>
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<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&lt;sub&gt;lip&lt;/sub&gt;</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-pediced 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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# Abbreviations – II

<table>
<thead>
<tr>
<th>Abbreviation</th>
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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>
</tr>
<tr>
<td>CMFP</td>
<td>CMF + prednisolon</td>
</tr>
<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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### Abbreviations – III

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<th>Abbreviation</th>
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</thead>
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<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>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>Acronym</th>
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<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>
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<tr>
<td>FEA</td>
<td>Flat epithelial atypia</td>
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<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>
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<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>
</tr>
<tr>
<td>GEICAM</td>
<td>Grupo Español de Investigación en Cancer de Mamma (Spanish Breast Cancer Research Group)</td>
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<tr>
<td>GnRHa</td>
<td>Gonadotropin releasing hormone analogue / agonist</td>
</tr>
<tr>
<td>GnRHa + AI</td>
<td>Gonadotropin releasing hormone analogue + aromatase inhibitor</td>
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<tr>
<td>GOS</td>
<td>Goserelin (Zoladex®)</td>
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<tr>
<td>Gy</td>
<td>Gray</td>
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<tr>
<td>Hand-Foot-Sy.</td>
<td>Hand-foot-syndrome</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<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>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
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## Abbreviations – V

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</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>ICH</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>
</tr>
<tr>
<td>ITA</td>
<td>Italian Tamoxifen Anastrozole Trial</td>
</tr>
<tr>
<td>JCO</td>
<td>Journal of Clinical Oncology</td>
</tr>
<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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<td>LABC</td>
<td>Locally advanced breast cancer</td>
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<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>LHRH</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>
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<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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# Abbreviations – VI

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<tr>
<th>Abbreviation</th>
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<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 Toxicitiy 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>
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<tr>
<td>NSABP</td>
<td>National Surgery Adjuvant Breast and Bowel Project</td>
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<tr>
<td>NSABP B14</td>
<td>NSABP Breast trial 14</td>
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<tr>
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<td>NSABP Breast trial 17</td>
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<td>NSABP B20</td>
<td>NSABP Breast trial 20</td>
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<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

OAS  Ovarian ablation or suppression
OFS  Ovarian function suppression
ONJ  Osteonecrosis of the jaw
OP  Operation
OR  Odds-ratio
ORR  Overall response rate
OS  Overall survival
OSNA  One-step nucleic acid amplification
Oxford  Oxford Centre for Evidence-based medicine levels of evidence and grades of recommendations

P + L  Paclitaxel + lapatinib
P weekly, Pw  Paclitaxel weekly
p.o., PO  Per os
Pac + Cap  Paclitaxel + capecitabine
PAI-1  Plasminogen-activator inhibitor type I
PAP  PAP-Smear (Papanicolaou), cytologic test of the uterine cervix
PBI  Partial breast irradiation
PEG-Liposomal Doxo  Pegylated liposomal doxorubicin
PET  Positron emission tomography
PFS  Progression free survival
PgR  Progesterone receptor
PMMA  Polymethylmethacrylate
PMRT  Postmastectomy radiotherapy
Pos. Cells  Positive cells
prosp.-rand. Phase III  Prospective and randomized phase III
PS  Performance score
PST  Primary systemic therapy
Pts.  Patients
## Abbreviations – VIII

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</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>
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## Abbreviations – IX

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

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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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Options for Primary Prevention: Modifiable Lifestyle Factors
Prevention

- **Version 2011:** Gerber / Thomssen
- **Versions 2012–15:** Dall / Diel / Gerber / Maass / Mundhenke
- **Version 2016:** Dall / Maass
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

- no weight gain: HR 1.00
- >10% weight gain: HR 1.24 (1.00-1.53)
- BMI 30-34.99: HR 1.40 (1.05-1.86)
- BMI >35: HR 1.41 (1.02-1.62)

- no alcohol: HR 1.00
- daily alcohol: HR 1.28 (1.091-1.62)

- phys. activity
  - none: HR 1.00
  - < 17.4 MET-h/wk: HR 0.81 (0.71-0.93)
  - > 17.4 MET-h/wk: HR 0.71 (0.61-0.82)

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

<table>
<thead>
<tr>
<th></th>
<th>2a</th>
<th>B</th>
<th>++</th>
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<tbody>
<tr>
<td>Maintaining normal weight (BMI at 18.5 – 25 kg/m²)</td>
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<td></td>
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<tr>
<td>Premenopausal</td>
<td>3a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Prevention/Screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>
Prevention by Changing Lifestyle Factors: Diet

- Preference of a healthy diet

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

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

* Recommended as a part of healthy nutrition
Prevention by Modifying Lifestyle Risk Factors: Alcohol

- Reduction of alcohol intake reduces risk of breast cancer 2b B

Particularly for
- ER+/PgR+ tumors 2b B
- Invasive lobular tumors 2b B
Prevention by Modifying Lifestyle Risk Factors: Smoking

- 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)

Oxford / AGO
LoE / GR
2a B ++
Prevention by Modifying Lifestyle Risk Factors: Physical Activity

- Physical exercise

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

Oxford / AGO
LoE / GR

2a(-)  B  ++
Prevention by Modifying Lifestyle Risk Factors:
Hormone Therapy in Postmenopausal Women

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

Oxford / AGO LoE / GR

1b A +

1b A +/-
# 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, 1.4 (1.1-1.9) insults, 2.1 (1.4-3.3) pulmonary embolism, 2.1 (1.5-2.9) deep vein thrombosis</td>
</tr>
<tr>
<td>WHI: JAMA 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HERS</strong></td>
<td>I 2763</td>
<td>1.2 (0.95-1.5)</td>
<td>med. age 67 J, no secondary prevention, side effects as compared to WHI + cholcystectomy</td>
</tr>
<tr>
<td>Hulley S: JAMA 2002</td>
<td></td>
<td></td>
<td></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. Tibolon RR 1.45 (1.2-1.7)</td>
</tr>
<tr>
<td>Beral V: Lancet 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPIC</strong></td>
<td>1.153 747</td>
<td>1.4 (1.2-1.6), 1.8 (1.4-2.2)</td>
<td>E-Mono, EPC &gt; E</td>
</tr>
<tr>
<td>Int J Cancer 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metaanalyse</strong></td>
<td>16 Studien</td>
<td>1.21-1.40</td>
<td>side effects as compared to WHI</td>
</tr>
<tr>
<td>Nelson HD: JAMA 2002</td>
<td></td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>Case-Control-Study, retrospect. Australia</td>
<td></td>
<td>2.09 (1.57-2.78)</td>
<td>current user</td>
</tr>
<tr>
<td></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>
</tr>
<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:
Secondary Prevention, Lifestyle and TNBC Subgroup (6/17)

No further information

No references
Secondary Prevention, Lifestyle and ER-positive Subgroup (7/17)

No further information

No references
Prevention by Changing Pregnancy Related Factors (8/17)

No further information

References:


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 2003–2015:**
  Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Rody / Thomssen / Schmidt

➢ **Version 2016:**
  Schmutzler / Stickeler
Principles in Prevention

- Women at increased risk for breast cancer are not considered patients but healthy women or counselees.

- A comprehensive informed consent taking into consideration all potential side effects and risks is warranted prior to offering preventive measures.

- Highest priority: „First, do no harm!“
  
  *(Primum nil nocere)*
Who Should be Tested for BRCA1/2 Mutations?

Families with
at least three women with breast cancer independent of age or
at least two women with breast cancer, one < 51 yrs. or
at least one woman affected by breast and one by ovarian cancer or
at least one woman affected by breast and ovarian cancer or
at least two women affected by ovarian cancer or
at least one woman affected by bilateral breast cancer, first < 51 yrs. or
at least one woman affected by breast cancer < 36 yrs. or
at least one man affected by breast cancer and one additional relative
affected by breast or ovarian cancer* #

* in one side of the family

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate ≥ 10% in ~25,000 families tested by 2015
Suggested Use of a Screening Checklist *

![Screening Checklist Image]

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

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

Regardless of age *

* Study participation recommended

* The rate of BRCA 1/2 mutation is decreasing with increasing age
### Mutation Prevalences in TNBC

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

Couch et al. JCO DOI 10.1200/JCO.2014.57.1414
State of the Art

Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity

- **High risk genes (OR >5.0)**
  - (BRCA1/2)

- **Moderately penetrant risk genes (OR 1.5 - 5.0)**
  - (RAD51C, ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, 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

79 common SNPs
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></td>
</tr>
<tr>
<td></td>
<td></td>
<td></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; Endometrial: ~ 25-60 % 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>&gt; 30 %&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></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 counselling: GCP
Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

**BROCA 40 gene panel**
(APC, ATM, BAP1, BARD1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, EPCAM, FAM175A, GALNT12, GEN1, GREM1, HOXB13, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53)

**AMBRY Genetics BreastNext (16 genes)**
(AIP, ALK, ATR, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCA, FANCC, FANCD2, FANCE, FANCJ)

**CEGAT CAN02: Brust- und Ovarialkarzinom (30 genes)**
(AMBRY Genetics BreastNext (16 genes) + APC, ATM, BAP1, BARD1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, EPCAM, FAM175A, GALNT12, GEN1, GREM1, HOXB13, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53)

**TruSight™ Cancer (Illumina)**
(AML1, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH2, MSH6, MUTYH, NBN, PMS2, PTEN, RAD50, RAD51C, STK11, TP53)

**CENTOGENE BC/OC panel (16 genes)**
(APC, ATM, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53)

**MYRIAD myRISK Panel (25 genes)**
(APC, ATM, BAP1, BARD1, BMPR1A, CDH1, CHEK2, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53)

For further information, visit the websites for each panel:
- [BROCA 40 gene panel](http://www.ambrygen.com/tests/breastnext)
- [AMBRY Genetics BreastNext](http://www.ambrygen.com/tests/breastnext)
- [CEGAT CAN02: Brust- und Ovarialkarzinom](http://www.cegat.de/Tumorerkrankungen_171.html)
- [TruSight™ Cancer (Illumina)](http://res.illumina.com/documents/products%5Cdatasheets%5Cdatasheet_trusight_cancer.pdf)
- [CENTOGENE BC/OC panel](https://www.centogene.com/centogene)
- [MYRIAD myRISK Panel](https://myriad-genetics.com/products/myr-risk-panel)

References:
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)
4 HNPCC genes (~1% of unselected OC cases show truncating mutations; Song et al., 2014)
20 BC/OC ´research genes

Strategy:

➢ Validation in large cohort, constant expansion and improvement
Genotype determines not only disease penetrance but phenotype and clinical disease course.

*Meindl et al. Nat. Genet 2010
Gevensleben et al. 2013
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

- 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)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Probability of being pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>0.95–0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>0.05–0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely not pathogenic or of little clinical significance</td>
<td>0.001–0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not pathogenic or of no clinical significance</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>3b</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>
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

Oxford / AGO
LoE / GR
GCP C ++
Definition of Women at Moderate to High Risk

- Deleterious mutation in the BRCA1, BRCA2
- Heterozygous risk of $\geq 20\%$ or remaining life time risk of $\geq 30\%$ acc. to a validated standard risk prediction model
- Childhood cancer survivors after chest irradiation in adolescence (e.g. Hodgkin disease)

Oxford / AGO
LoE / GR

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
</tr>
</tbody>
</table>
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 2a B ++

- Clinical breast exam >=25 years semi-annually
- Sonography >=25 years semi-annually
- Mammography >=40 years biannual
- Breast MRI (until ACR1) >=25 years annual

For mortality reduction (10 year survival) 3 B +

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

Oxford / AGO
LoE / GR

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

2a B ++

Oxford / AGO LoE / GR

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

5  D  +

3b  C  +
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
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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk-reducing bilateral salpingo-oophorectomy (RR-BSO, PBSO) around 40 years of age</td>
<td>2a B ++*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral mastectomy (RR-BM, PBM)</td>
<td>2a B +*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **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

- **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*


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 +

- BRCA1/2 mutation status is predictive for chemotherapy response 3b B +

- Carboplatin (vs. Docetaxel) in MBC 2b a B +

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

+ Overall prognosis has to be considered

*Study participation recommended
BRCA mutations, therapy response and prognosis in the neoadjuvant GeparQuinto


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

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

for the GBG/AGO-B study groups
Medical Prevention for Women at Increased Risk

- **Tamoxifen for women > 35 years**
  Reduction of invasive BrCA, DCIS, and LN
  - 1a A +*

- **Raloxifen for postmenopausal women**
  Reduction of invasive BrCa only
  - 1b A +*

- **AI for postmenopausal women**
  - 1b A +#

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

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

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

- Tamoxifen*
- Aromatase inhibitors*
- Suppression of ovarian function* + Tamoxifen

*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
- Genetic testing
- Prophylactic surgery
- Stratified therapy

**Communication, Exchange, Advice**
- Certified BC Ctr
- Familial BC Ctr

**Genetic testing**

* trans-sectoral contract for integrated care, acc. to code of social law § 140a since 2015
Breast Cancer Risk and Prevention (2/35)

*Further information:*

Literature from PUBMED, ASCO- and SABCS-abstracts

*No references*
Principles in Prevention (3/35)

No further information

No references
Who Should be Tested for BRCA1/2 Mutations? (4/35)

No further information

References:

2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of up-dated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%.
**Suggested Use of a Screening Checklist (5/35)**

*No further information*

*No references*
BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (6/35)

Further information:

TED poll:
N=5 , as predictive marker
N=21 ,,impact"
N=3, omit
N=9 ++
N=21 +

References:

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


Mutation prevalences in TNBC (7/35)

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

References:

No further information

No references
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (9/35)

No further information

References:

2. Tan et al., Lifetime cancer risks in individuals with germline PTEN mutations, Clin Cancer Res. 2012 Jan 15;18(2):400-7

Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction (10/35)

No further information

No references
TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC (11/35)

*No further information*

*No references*
Clinical Implication: Genotype/Phenotype (12/35)

No further information

References

Genetically Defined Subtypes are Distinct Tumor Entities (13/35)

No further information

References:


VUS: Problems and Questions (14/35)

No further information

References

Variant classification proposed by IARC (15/35)

No further information

References:

Classification of IARC class 3 variant (16/35)

No further information

References:

1. ENIGMA – evidence-based network for the interpretation of germline mutant alleles: an international interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. Human Mutat 33: 2-7, 2012
Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (17/35)

No further information

References:

Current Clinical Impact of non-BRCA1/2 Breast Cancer Risk (NBBC) (18/35)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (19/35)

No further information

No references
Definition of Women at Moderate to High Risk (20/35)

No further information

References:

Surveillance Program for Female for Women with deleterious BRCA-mutations (21/35)

Further information and references:


The German Consortium for Hereditary Breast and Ovarian Cancer has established an intensive surveillance program that is offered to mutation carriers and women at high risk within the 12 centres of familial breast and ovarian cancer in

These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).

The surveillance program allows the detection of early stage breast carcinomas (MARIBS study group Lancet 2005, Kriege et al. NEJM 2004, Warner et al. JAMA 2004, Kuhl, Schmutzler et al. 2000 ). However, no data exist so far on long term follow-up and mortality reduction.

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

No further information

References:

Surveillance Program for Female Carriers of Pathogenic BRCA Mutations after Primary Breast Cancer acc. to GC-HBOC (23/35)

No further information

References:

Surveillance for Male Carriers of Pathogenic BRCA Mutations acc. to GC-HBOC (24/35)

No further information

References:

Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease (25/35)

Further information and references:

5. Leach MO et al. Lancet 2005


These guidelines are in close agreement with the NICE-guidelines on Great Britain (McIntosh A et al.: Clinical Guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: national Collaborating Centre for Primary Care/University of Sheffield, 2004).

Surgical Prevention (26/35)

No further information

References:

Surgical Prevention for Healthy BRCA1/2 Mutation Carriers (27/35)

Further information and references:

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-krbshilfe.de)
Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (28/35)

No further information

References

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

*No further information*

**References:**

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

**Further information and references:**

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

3. L. et al. JCO 2006
At present, the German consortium for hereditary breast and ovarian cancer recommends surgical and adjuvant therapy of hereditary breast cancer according to standard guidelines.

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

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

BRCA1 associated breast cancers have a poor prognosis that is mitigated by adjuvant chemotherapy (Robson et al. Breast Cancer Res 2003). Moreover, in vitro studies suggest a distinct chemosensitivity profile of BRCA associated breast carcinomas (Lafarge et al. Oncogene 2001, Quinn et al. Cancer Res 2003). Recent data suggest the benefit of new
therapeutic strategies that need to be further proven by RCTs. Therefore, affected BRCA mutation carriers and women at high risk should be referred to the centres for familial breast and ovarian cancer.
No further information

No references
Early survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer (GeparSixto) (32/35)

No further information

No references
Medical Prevention for Women at Increased Risk (33/35)

No further information

References:


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

Further information:

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

No references
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (35/35)

No further information

No references
Early Detection and Diagnosis
Early Detection and Diagnosis

➢ **Versions 2005–2015:**
  Albert / Blohmer / Fersis / Junkermann / Maass / Scharl / Schreer

➢ **Version 2016:**
  Schreer / Albert
# 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>40–50</td>
<td>12–18</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>50–70*</td>
<td>24</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>&gt;70</td>
<td>24</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

* National Mammography-Screening-Program
## Breast Cancer Mortality Reduction

### Meta-Analyses

<table>
<thead>
<tr>
<th>Source</th>
<th>Methodology</th>
<th>RR 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent UK Panel, 2012</strong></td>
<td>13-year metaanalysis</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td><strong>Cochrane Review, 2011</strong></td>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<td></td>
<td>As above, but excluding women &lt;50 years</td>
<td>0.77 (0.69–0.86)</td>
</tr>
<tr>
<td><strong>US Task Force, 2009</strong></td>
<td>Women 50–59 years</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td></td>
<td>Women 60–69 years</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td></td>
<td>Estimates weighted average</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Canadian Task Force, 2011</strong></td>
<td>Women aged 50–69 years</td>
<td>0.79 (0.68–0.90)</td>
</tr>
<tr>
<td><strong>Duffy et al., 2012</strong></td>
<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>Case-Control Studies</th>
<th>Incidence-based Mortality Studies</th>
<th>Randomized Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broeders et al</td>
<td>Broeders et al</td>
<td>Gotsche and Jorgenson</td>
</tr>
<tr>
<td>Screening Mx</td>
<td>Screening Mx</td>
<td>Screening Mx</td>
</tr>
<tr>
<td>Corr. for self selection</td>
<td>0.62 (0.56-0.69)</td>
<td>0.81 (0.74-0.87)</td>
</tr>
<tr>
<td>Invited for screening</td>
<td>0.69 (0.57-0.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></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
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) 0.74 (95%CI 0.66-0.83)
40–44 J 0.83 (95%CI 0.67-1.00)
45–49 J 0.68 (95%CI 0.59-0.78)
Participants 0.71 (95%CI 0.62-0.80)

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

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

Screening-Breast Sonography
  - Automated 3D-Sonography

As an adjunct:
  - Dense mammogram (ACR 3–4)
  - Elevated risk
  - Mammographic lesion
  - Second-look US (MRI-only detected lesions)

Oxford / AGO
LOE / GR

- Screening-Breast Sonography: 5  D  - -
- Automated 3D-Sonography: 3b  C  - -
- Dense mammogram (ACR 3–4): 2b  B  ++
- Elevated risk: 1b  C  ++
- Mammographic lesion: 2b  B  ++
- Second-look US (MRI-only detected lesions): 2b  C  ++
# Early Detection
## Clinical Examination

<table>
<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>As stand alone procedure</td>
</tr>
<tr>
<td>Self-examination</td>
</tr>
<tr>
<td>Clinical breast examination (CBE) by health professionals</td>
</tr>
<tr>
<td>CBE because of mammo/sonographic lesion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBE in combination with imaging</td>
</tr>
</tbody>
</table>

* 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</td>
<td>B</td>
</tr>
<tr>
<td>Mammography</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Additional Tomosynthesis (vs spot compression)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Sonography</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Elastography (shear-wave)</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Automated 3D-sonography</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>MRI*</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Minimally invasive biopsy</td>
<td>1c</td>
<td>A</td>
</tr>
</tbody>
</table>

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

- **Clinical examination**
  - Oxford 5 D ++
  - AGO

- **Mammography**
  - Oxford 2b B ++
  - AGO

- **Mammography**
  - Oxford 3b B +
  - AGO
  - added MRI
    - Oxford 3b B -
    - AGO

- **Sonography**
  - Oxford 2b B ++
  - AGO

- **Axilla + FNP/CNB**
  - Oxford 2b B ++
  - AGO

- **MRI**
  - Oxford 1b B +/-
  - AGO

- **Minimally invasive biopsy**
  - Oxford 1b A ++
  - AGO

* Weak reduction in reexcision rate in lobular-invasive cancer but sign. higher rate of initial mastectomy. Lobular invasive tumors, suspicion of multilocular disease, high-risk patients. MRI-guided vacuum biopsy mandatory in case of MRI-detected additional lesions.

** If clinical examination, mammography and sonography (e.g. plus MRI) do not allow assessment of lesion extension
MRI: Preoperative Staging

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

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>MRT</th>
<th>Mammographie</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></td>
<td></td>
</tr>
<tr>
<td>Warner 2004</td>
<td>M</td>
<td>236</td>
<td>22</td>
<td>77</td>
<td>95</td>
<td></td>
<td></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></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></td>
<td></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>
</tr>
<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>
</tr>
<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 - 2015
- Medline 2013 – 2015
- Cochrane 2013 - 2015

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

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies
Further information:

The aim of early detection and screening of breast cancer is to reduce the risk of dying from the disease. Detecting invasive breast cancer at an early stage (Stage I-IIA) offers the chance of survival with less treatment impairment and better quality of life. Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false positives, false negatives, overdiagnosis and overtreatment.

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

Data from observational studies and registries:
The EUROSCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: 1. “the best “European” estimate of of breast cancer reduction is 25-31% for women invited for screening, and 38-48% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis”.
The population-based data from the United States (SEER-Cancer Statistics 1976 - 2009) showed an marked increase in early-stage breast cancer (DCIS and localised breast cancer) and a reduction of late-stage cancer of 37% compared with the prescreen trends.
Since 2006 mammography screening is offered to women age 50-69 in Germany within a population-based organised quality assured program in accordance with the European Guidelines for Quality Assurance in Mammography Screening.
References:

40. 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:

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

No further information

No further references
Breast cancer screening – Viewpoint of the IARC Working Group (8/19)

No further information

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.

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
**Early Detection Sonography (10/19)**

*Further information:*

The arguments against ultrasound use as stand alone screening modality are reproducibility, high false-positive rate, low ppv for biopsy, inability to detect most DCIS cases, operator dependency and lack of quality assurance.

Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permits detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group are associated with an increased recall and biopsy rate. Supplemental ultrasound is associated with increasing costs. Modeling suggests for women between the ages of 50 and 74 years with heterogeneously or extremely dense breast tissue may avert only 0.4 breast cancer deaths but result in 354 additional biopsy recommendations per 1000 women screened compared with biennial screening mammography alone, with a cost-effectiveness ratio of $325 000 per quality-adjusted life-year gained (Sprague BL, et al 2015).

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

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

**References:**


Further information:

In a large well performed randomized study no difference in breast cancer mortality emerged after 11 years of follow-up. The only difference was that women in the self-examination arm had nearly twice as many biopsies for benign lesions than women in the control arm. Therefore based on current evidence breast self-examination cannot be recommended anymore. No randomized studies have been performed, where screening-examination by health professionals is compared to no screening. One Japanese case-control study suggests that examination by health professionals might reduce mortality from breast cancer. A randomized trial in Canada showed no difference in breast cancer mortality between a group of women offered clinical breast examination or mammography combined with clinical breast examination. Nevertheless in asymptomatic women participating in mammography screening programs there is the risk of interval cancer development. This is the reason why in the US mammography screening is recommended in close connection with clinical examination. Recent data (Haakinson and coauthors 2010) underscore this strategy. The ACS updated Guideline 2015 does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. The IARC Working Group states that there is inadequate evidence for a reduction of breast cancer mortality.

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:


3. Elizalde A, Pina L, Ebrano J, Slon P, Zalazar R, Caballeros M. Additional ultrasound or DBT after digital mammography: which one is the best combination? Acta Radiol 2016;57(1)13-18


**Tomosynthese**


**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:


11. 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
13. Lourenco AP, Mainiero MB Incorporating imaging into the locoregional management of breast cancer. Semin Radiat Oncol 2016;26(1)
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
years on breast cancer mortality a 10 years follow-up: a randomised controlled trial. The Lancet 2006; 368: 2053 – 2060


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:


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


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

*No further information*

*No references*
MRI and DCIS (19/19)

No further information

References:

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Pathology
Pathology

- **Versions 2004–2015:**
  Costa / Fehm / Friedrichs / Huober / 
  Kreipe / Lück / Sinn / Thomssen

- **Version 2016:**
  Blohmer / Kreipe
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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</table>
Use of Fine Needle Aspiration Cytology*

- Nipple secretion
- Tumor
- Cyst
- Lymph node

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<tr>
<th>Case</th>
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<tbody>
<tr>
<td>Nipple secretion</td>
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<td>Tumor</td>
<td>5 D -</td>
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<tr>
<td>Cyst</td>
<td>5 D +/-</td>
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<tr>
<td>Lymph node</td>
<td>5 D +/-</td>
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</table>

* Ultrasound-guided core biopsy recommended
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)

- Routine workup in step sections (14G: 3 sections / 11G, 8G: 6–8 sections)  
  **Oxford / AGO LoE / GR**: 5 D ++

- Correlation with imaging (density, calcifications), use of B-classification  
  **Oxford / AGO LoE / GR**: 1b B ++

- Frozen section diagnosis on core biopsies  
  **Oxford / AGO LoE / GR**: 5 D - -

- Routine evaluation of ER/PgR and HER2 status  
  **Oxford / AGO LoE / GR**: 3b C ++

- Turn-around time < 24 h (histology)  
  **Oxford / AGO LoE / GR**: 5 D +
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
### Workup: Mastectomy Specimens

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<tr>
<td><strong>Margins always to be sampled</strong></td>
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<tr>
<td>- Skin close to tumor, at least 2 directions</td>
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<tr>
<td>- Deep margin</td>
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<td>- Other margins, if close (&lt; 1 cm)</td>
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<tr>
<td><strong>Attention to soft tissue margins in skin sparing mastectomy</strong></td>
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<tr>
<td><strong>Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region</strong></td>
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<tr>
<td><strong>More extensive sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)</strong></td>
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# Workup: Sentinel Node Biopsy

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

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<th>Oxford / AGO LoE / GR</th>
<th>Indication</th>
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<tr>
<td>5        D       +</td>
<td>Sentinel node biopsy for invasive cancer</td>
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<tr>
<td>5        D       +/-</td>
<td>If clinical consequence</td>
</tr>
<tr>
<td>5        D       +</td>
<td>If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)</td>
</tr>
<tr>
<td>5        D       +</td>
<td>Closest margin of resection</td>
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<tr>
<td>5        D       -</td>
<td>If macroscopically &lt; 1 cm</td>
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<tr>
<td>5        D       +</td>
<td>If macroscopically &gt; 1 cm</td>
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<tr>
<td>5        D       +</td>
<td>Lesions ≥ 1 cm, without core biopsy</td>
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<tr>
<td>5        D       -</td>
<td>Non-palpable lesions or lesions &lt; 1 cm</td>
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<tr>
<td>5        D       +</td>
<td>Asservation of fresh tissue (tumor banking)</td>
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</table>
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

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

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

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<th>AGO LoE</th>
<th>AGO Level</th>
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Reporting: pTNM

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

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


  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)
  
- Reporting of minimal distance to resection margin and topography thereof
  
- R-Classification

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
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

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- **Identification of tumor bed, otherwise ypTX**
  - 4  D  ++

- **Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma**
  - 4  D  ++

- **pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded**
  - 2b  D  +

- **Use of IHC to identify tumor residues**
  - 4  D  +/-

- **Reporting of ypTN after therapy**
  - 5  D  ++
Special Studies: ER-Testing by IHC

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

For therapeutic implications see chapter “Endocrine therapy”
### Special Studies: PgR-Testing by IHC

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<tr>
<td>Immunohistochemical detection on paraffin embedded (FFPE) tissue</td>
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<td>A</td>
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<tr>
<td>Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%)</td>
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<tr>
<td>Staining intensity of pos. tumor nuclei (0 - 3)</td>
<td>4</td>
<td>D</td>
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<tr>
<td>Allred Score (0 - 8), Remmele Score (0 - 12)</td>
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### Additional Special Studies: Molecular Analysis of ER/PgR Status

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<tr>
<th>Oxford / AGO LoE / GR</th>
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<td>Evaluation of hormone receptors using validated gene expression test kits</td>
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<td>Evaluation of hormone receptor by RNA-sequencing</td>
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<tr>
<td>Use of molecular receptor analysis for subtyping</td>
<td>5 D -</td>
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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

Oxford / AGO LoE / GR

1a A ++
3a C ++
3a C ++
3a C ++
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
  - Oxford / AGO LoE / GR
    
    | Therapy decision | Grade |
    |------------------|-------|
    | 1a A ++           |       |

- Evaluation of HER2 through using validated gene expression test kits
  - Oxford / AGO LoE / GR
    
    | Evaluation method         | Grade |
    |---------------------------|-------|
    | 3b B +/-                  |       |

- Evaluation of HER2-amplification by RNA-sequencing
  
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- Use of molecular HER2-testing for subtyping
  
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### Special Studies: Evaluation of Ki-67 Score

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<tr>
<td>Counting of tumor nuclei at the invasion front</td>
<td>5 D ++</td>
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<tr>
<td>Consideration of weakly stained tumor nuclei</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Reporting of Ki-67 positive nuclei as percentage</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Establishing of laboratory standards and cut-off values</td>
<td>5 D ++</td>
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<tr>
<td>Use of image analysis for objective Ki-67 evaluation</td>
<td>5 D +</td>
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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:


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 \(\geq 500 \, \mu\text{m}\) 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 ≥ 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

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%)

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: Immunohistochemistry (30/30)

No further information

No references
Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **Versions 2002–2015:**
  Costa / Fersis / Friedrichs / Gerber / Göhring / Harbeck / Janni / Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen

- **Version 2016:**
  Witzel / Nitz
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

1Simon et al, J Natl Cancer Inst 101: 1446-1452, 2009
2Febbo et al, J Natl Compr Canc Netw 9 Suppl 5: S1-32, 2011
## Elements of Tumor Marker Studies that Constitute Levels of Evidence Determination

<table>
<thead>
<tr>
<th>Category</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 utility</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</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study</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</td>
<td>Result more likely to be play of chance that A but less likely than C</td>
<td>Result very likely to be play of chance</td>
<td>Result very likely to be play of chance</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&lt;sub&gt;Ox2001&lt;/sub&gt;</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\textsubscript{Ox2001}</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\textsuperscript{®} ELISA)\textsuperscript{§} 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>

\textsuperscript{§} Validated clinical data only available for this assay
# Commercially Available Molecular Tests

<table>
<thead>
<tr>
<th>Provider</th>
<th>Type of assay</th>
<th>Type of tissue</th>
<th>Technique</th>
<th>Central lab</th>
<th>Indication and population studied</th>
<th>Clinical Validation</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agendia</td>
<td>70-gene assay</td>
<td>fresh frozen (technical validation for FFPE available)</td>
<td>Microarrays for RNA</td>
<td>yes</td>
<td>prognostic N-/+, &lt;61 Jahre</td>
<td>yes</td>
<td>FDA clearance as “In Vitro Diagnostic Multivariate Index Assay (IVDMIA)”</td>
</tr>
<tr>
<td>Genomic Health</td>
<td>21-gene recurrence score</td>
<td>FFPE</td>
<td>qRT-PCR</td>
<td>yes</td>
<td>prognostic N-/+, ER+ endocrine treated</td>
<td>yes</td>
<td>Clinical Laboratory Improvement Amendments (CLIA) + College of American Pathologists (CAP)-accredited ref lab</td>
</tr>
<tr>
<td>Sividon</td>
<td>11-gene assay</td>
<td>FFPE</td>
<td>q-RT-PCR</td>
<td>no</td>
<td>prognostic (pre-) postmenopausal N-/+, ER+ HER2- endocrine treated</td>
<td>yes</td>
<td>CE-Mark</td>
</tr>
<tr>
<td>NanoString</td>
<td>50-gene assay</td>
<td>FFPE</td>
<td>Direct hybridization</td>
<td>no</td>
<td>prognostic postmenopausal N-/+, ER+ HER2- endocrine treated</td>
<td>yes</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 (\text{MammaPrint}^\circ) $</th>
<th>21 gene Recurrence score (\text{Oncotype DX}^\circ)$</th>
<th>8 gene signature (\text{Endopredict}^\circ)$</th>
<th>PAM 50 (\text{Prosigna}^\circ)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis after 5 yrs (\text{late recurrences})</td>
<td>not separately shown</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Predictive impact (\text{chemotherapy benefit})</td>
<td>poorly validated</td>
<td>yes *</td>
<td>not shown</td>
<td>not shown</td>
</tr>
<tr>
<td>Prospective-retrospective evidence (% \text{of recruited patients})</td>
<td>Multicenter validation</td>
<td>NSABP B-14 (14%)</td>
<td>ABCSG 6 (19%)</td>
<td>MA.12 (59%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSABP B-20 (28%)</td>
<td>ABCSG 8 (36%)</td>
<td>MA.5 (66%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG 9127</td>
<td>GEICAM-9906 (45%)</td>
<td>ABCSG 8 (44%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SWOG 8814 (40%)</td>
<td>ATAC (30%)</td>
<td>ATAC (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATAC (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective evidence (\text{pending})</td>
<td>MINDACT (completed)</td>
<td>TAILOR(x) (\text{N0, low-risk, RS&lt;11})</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PlanB (\text{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
## 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&lt;sup&gt;®&lt;/sup&gt;) $</td>
<td>I</td>
<td>A</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**
  - (Oncotype DX<sup>®</sup>)
    - (N0-/+; HR+ HER2-, 5 Jahre)
    - LoE: I, CTS: A, AGO: +*
  - (EndoPredict<sup>®</sup>, Prosigna<sup>®</sup>)
    - (N-/+; HR+ HER2-)
    - LoE: I, CTS: B, AGO: +*

- 70 gene signature (MammaPrint<sup>®</sup>), N0-1
  - LoE: II, CTS: C, AGO: +*

- IHC4 (central pathology, published algorithm) #
  - LoE: I, CTS: B, AGO: +/-

* 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$_{Ox2001}$</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><em>PIK3CA</em> mutation</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 >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><strong>Endocrine therapy</strong></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><strong>Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 polymorphism</td>
<td>2b</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ovarian ablation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal status</td>
<td>1c</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors vs. Tamoxifen</strong></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_{Ox2001} (§ LoE_{Ox2009})</th>
<th>GR (§ CTS)</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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(_{2009})</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search®)</td>
<td>I</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Prognosis at baseline</td>
<td>I</td>
<td>A</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 (2/20)

Further information:


Guidelines screened:
- Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)

References:

Definition (3/20)

No further information

No references
Low Absolute Risk Implies Low Absolute Benefit (4/20)

Further information:

Adjuvant chemotherapy reduces breast cancer mortality by one third. However, the benefit is closely related to the absolute risk of this individual patient. Especially in low risk tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leukemia / MDS/ other secondary cancers. Because of this, proper risk assessment is mandatory. Adjuvant chemotherapy reduces breast cancer mortality by one third. Because of this, proper risk assessment is mandatory. In the MINDACT trial for example a group of international experts consented not to propose adjuvant chemotherapy in patients with an estimated distant metastasis free survival of 92% after five years.

References:

Quality Criteria (5/20)

Further information:

Ranking of evidence is of pivotal importance for clinical decision-making. The Oxford Levels of Evidence (LoE_{Ox2001}) and Grades of Recommendations (GR) were originally released in 2001 by the Centre of Evidence Based Medicine (www.cebm.net). These original Oxford LoE and Grades of Recommendation were modified in 2011. The authors simplified the Levels in several ways. For example, levels 1a-c were merged to level 1. The novel classification was also modified to represent the natural flow of a clinical encounter (diagnosis, prognosis, treatment, benefits, harms). These modified Oxford LoE also apply to prognostic factors. In this case, Level 1 can be reached with “systematic review of inception cohort studies”. Based on study quality and effect size, levels LoE can be graded up or down. Finally, the authors of the modified Oxford LoE state, that “levels be interpreted with a healthy dose of common sense and good judgment”.

To improve the quality of research on biomarkers a guideline named REMARK (Reporting Recommendations of Tumor Marker Prognostic Studies) was defined. REMARK describes the informations which should be given when publishing a biomarker study such as study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. Depending on the quality of a biomarker study, the Tumor Marker Utility Grading System was introduced assigning different levels of evidence to a certain marker. To obtain the highest level of evidence, a marker had to be tested prospectively in a prospectively randomized clinical study. Recently a refined system for biomarker study design and evaluation that incorporates a revised level of evidence scale for tumor marker studies, including those using archived specimens, was introduced. Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly, so more efficient indirect "prospective–retrospective" designs using archived specimens might reach level I evidence if validated with consistent results. This recommendation was recently elaborated on and finally resumed by the NCCN Task Force Report for evaluation of the clinical utility of tumor markers in oncology.
In this chapter on prognostic and predictive factors the original Oxford LoE and the revised classification of Levels of Evidence using elements of tumor marker studies as proposed by Simon, Paik and Hayes, 2009 are used as applicable.

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

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

No further information

References:

2. Canadian Medical Association (CMA, 2006: http://www.cmaj.ca/cgi/content/full/158/3/DC1)

Statement: Obesity

Reproducibility (10/20)

Further information:

Conventional pathology and immunohistochemistry is for methodological reasons subject to high inter-observer variability/variable reproducibility. However, comparison of large series in recently conducted trials show high concordance for HR status in central and local pathology, whereas discordances for Ki-67 and grading are clinically meaningful. HER2 discordances in German trials are observed in up to 10% of cases. In the ASCO-CAP guidelines Her2 discordances are reported in up to 6% of cases. In the landmark trials a small number of patients tested HER2-negative by IHC derive some benefit from trastuzumab. For grading a concordance in about 68% of cases in German trials was seen. MIRROR trialists report upgrading of N0 status by central pathological review in an comparable amount. A high inter- and intraobserver variability in measurement of the proliferation marker ki-67 has been described. Preanalytical and analytical assessment is not standardized. Thus the clinician should be aware of potential problems and pitfalls when decision for adjuvant treatment is taken together with the patient.

References:


Critical Issues regarding LoEs for Biomarkers (11/20)

No further information

No references
Prognostic Factors II in Early Breast Cancer (12/20)

Further information:

St Gallen Consensus accepted a cut-off for Ki-67 of 20%.
Semiquantitative IHC expression of PR (< 20%) adds prognostic value with the current IHC based luminal A definition (for cut-off Ki-67 14%)

References:

ER/PR

HER2
Ki-67


uPA/PAI-1


Post treatment ki 67:
Commercially Available Molecular Tests (13/20) and (14/20)

Further information:

Modern genomic platforms generate highly reproducible information about tumor biology, which has to be integrated during the next years into clinical routine. Since the additive clinical information is highly correlated to the validation sets the commercially available tests have been enumerated separately together with their retrospective-prospective evidence. ASCO-guidelines already integrated uPA/PAI1 and Oncotype DX®. There is new retrospective evidence from the prospective ATAC trial involving 928 patients from the ATAC trial (> 9000 patients) conducted in postmenopausal women (Trans ATAC). In this cohort EP and EP clin were highly prognostic for distant recurrence in endocrine treated patients with ER+/HER2- disease. EPclin provided more prognostic information than RS, particularly after 5 years follow-up and in node positive patients.

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

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

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

Endopredict


Mammaprint


Oncotype


PAM50


**Prognostic Factors III in Early Breast Cancer (15/20)**

No further information

**References:**

**DTC**


CTC


Oncotype


Endopredict


PAM50


IHC4


Neoadjuvant Systemic Chemotherapy – Response Prediction I (16/20)

Further information:

This slide is based on the evidence mainly from analyses done by GEPAR- trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides. Ki 67 data from GEPARTRIO have been updated by Denkert et al. (Ann Oncol 2013) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations. For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs. The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

References:

TIL


PIK3CA Mutation
Neoadjuvant Systemic Chemotherapy – Response Prediction II (17/20)

No further information:

References:

TIL


PIK3CA


Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides sample evidence that hormone receptor status is predictive for endocrine response, whereas little effect can be attributed to tumor size, nodal status, age and grading. According to the ASCO /CAP guidelines the panel recommended endocrine therapy in patients whose breast tumors show at least 1% ER positive cells. Same is true for PG receptor levels. HER2 overexpressing tumors present primarily with more aggressive biology. HER2 overexpression, quantitative ER and PR expression as single markers do not identify patients with better outcome after AI, when compared to TAM. (Dowsett M)

Cyp2D6 polymorphism detection is not recommended in daily routine as the metaanalysis done by Goertz is not conclusive.

ABCSG12 trialists, who compared AI + Goserelin vs Tam in premenopausal women report a nearly 50% increase in the risk of disease recurrence (HR 1.49) and a three-fold risk of death for overweight patients (BMI > 25) receiving AI+ Gos in comparison to TAM. In postmenopausal women ATAC trialist report a nonsignificantly better relative benefit of AI vs Tam in thin women vs overweight women (BMI > 35).

A retrospective analysis from a representative subgroup of more than 2500 patients from BIG 1-98 demonstrated a strong correlation of AI superiority with invasive lobular histology and luminal B like tumors (ER+/PR+/Ki 67 >14, HER2-). The HR were 0.95 for ductal luminal A, 0.64 for ductal luminal B, 0.49 for lobular luminal A and 0.33 for lobular luminal B.

References:

amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95


Predictive Factors – HER2 Targeted Therapy / Adjuvant Chemotherapy (19/20)

Further information:

HER2 overexpression (IHC, ISH) is highly predictive for anti HER2 therapy. During SABCS 2012 Baselga presented biomarker analyses evaluating patients with higher benefit from addition of pertuzumab from the CLEOPATRA trial. Neither HER2 or HER3 (mRNA), nor EGFR (mRNA) were predictive.

The last EBCTCG metaanalysis involving over 100,000 chemotherapy patients from 123 randomized trials demonstrated proportional risk reduction little affected by age, nodal status, tumor diameter, HR status and grading. The evidence for HER2 overexpression is much less well evaluated. Most data are derived from trials evaluating chemotherapy + endocrine therapy versus endocrine therapy alone in HR+ patients (Viale IBCSG VIII + IX, Albain SWOG 8814 and Paik NSABP B-20). Uniformly the degree with chemotherapy interaction is non significant independently whether evaluated by central DAKO Hercept testing or her2 gene group as part of Oncotype DX.

The prospectively randomized chemo N0 trial demonstrated that high levels of upA/PAI-1 are associated to increased CMF chemotherapy benefit. In N0-1/HR+ patients the same has been demonstrated by retrospective analyses from the prospective trials NSABP – B20 and SWOG 8814 for CAF/Tam vs Tam alone. In N0 patients from B-20 the RR was 0.26, 0.61 and 1.31 for high risk, intermediate risk and low risk patients, with an net chemotherapy benefit of 28% 10 year distant free survival benefit in the high risk group. In SWOG 8814 evaluating N+ patients the HRs for 5 yr overall survival were 0.56 in the high risk group, 0.84 in the intermediate and 1.18 in the low risk group resulting in a net 10 yrs dfs benefit of 12% for the high risk group.

Data for Mammaprint (Knauer et al) refer to 541 patients from pooled study series from patients who received endocrine therapy +/- chemotherapy. In the high risk group the univariate HR was 0.21 (p < 0.01) compared to 0. 58 (p= 0.6) in the low risk group. For other genomic signatures there are no data. PAM50 has been only evaluated in a neoadjuvant setting as surrogate parameter for pCR and Endopredict data refer to patients treated with endocrine therapy only.
Baseline Ki-67 is as Viale et al demonstrated from retrospective analyses of two IBCSG trials no independent predictor of chemotherapy outcome. Retrospective subgroup analyses of patients from large taxane trials (GEICAM, PACS 01, BCIRG 01, EC-Doc) demonstrate that luminal A like tumors identified by IHC are likely to have small benefit, but these third generation trials do not have endocrine only arms. HER2 overexpression was highly predictive for anthracyline outcome when compared to CMF. In a subgroup of the patients analysed by Gennari Di Leo published a metaanalysis comparing the impact of Her2 status and TOP2A (FISH). The HR for her2 amplification and non amplification were 0.89 and 0.71 respectively. Those for Topo normal versus Topo altered were 0.88 vs 0.64 respectively. TOP2A coamplification, not HER2 amplification, is the clinically useful predictive marker of an incremental response to anthracycline-based chemotherapy. Response to taxanes has been evaluated in different third generation trials comparing anthracycline based chemotherapy vs taxane/anthracycline based regimens. Identification of low proliferating tumors by central ki-67 evaluation was predictive for taxane outcome in EC-Doc, BCIRG 001 and PACS 001, but not in the GEICAM trial. Endopredict and Oncotype DX did not predict taxane response in the GEICAM trial and in NSABP B28 respectively.

No references
Prognostic factors – Metastatic breast cancer (20/20)

Further information

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

References:

CTC


Lesions of Uncertain Malignant Potential (B3)

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

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

- **Version 2016:**
  Friederichs / Sinn
B-Classification*

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

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

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

- Inhomogenous lesions with sampling risk:
  - Phyllodes tumor, cellular fibroadenoma
  - Atypical papilloma, if incompletely removed
  - Radial scar, complex sclerosing lesion
Major B3-Lesions and Prospektive Prediktive Value (PPV) for Malignancy in Resection

B3-Lesions: ~PPV

- Atypical ductal hyperplasia (ADH) 20-30%
- Lobular intraepithelial neoplasia (LN/LIN) 0-10%
- Flat epithelial atypia (FEA) 0-10%
- Radial scar / Complex sclerosing lesion 0-10%
- Papilloma without atypia 0-10%
- Cellular fibroepithelial tumors / phyllodes tumors 0%
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 ++
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
Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)

### Stratification of breast cancer risk*

- **Number of Foci:**
  - 1  RR = 2.33
  - 2  RR = 5.26
  - ≥ 3 RR = 7.97

- **Microcalcifications:**
  - present RR = 3.21
  - not present RR = 4.21

- **Type**
  - ductal RR = 3.83
  - lobular RR = 3.67
  - both RR = 7.10

- **Age**
  - < 45 RR = 6.76
  - 45 – 55 RR = 5.10
  - > 55 RR = 2.67

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

  2b  C  ++

- **LIN at margins of resection specimen (BCT):**
  - No further surgery

  Exceptions:
  - a) Pleomorphic LIN, florid LIN, or LIN with necrosis
  - b) Imaging abnormality is not removed

  → Complete resection

  5  D  ++

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

- **FEA at margins in resection specimen:**
  - No further surgery, unless calcifications have not been completely removed
  
  - **Oxford / AGO LoE / GR**
    - 3b C ++

---

* Terminal ductal-lobular unit
Papilloma

- **Includes:** Central and peripheral papilloma $>$ 2 mm, atypical intraductal papilloma (B3)
- To be discriminated from peripheral micropapilloma arising in the TDLU, size $\leq$ 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

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

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

  - Oxford / AGO LoE / GR
    - 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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>5</th>
<th>C</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
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<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>
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>Fractures</td>
<td>2.88</td>
<td>1.97</td>
<td>0.91</td>
<td>0.51-0.92</td>
</tr>
<tr>
<td>Endometrium 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 Lebensjahr
- With enhanced risk for thrombembolism
Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen, Side Effects)

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

<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>
<td>68</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>0.74</td>
<td>0.58-0.94</td>
<td>12</td>
<td>81</td>
</tr>
<tr>
<td>Thrombembolism</td>
<td>1.72</td>
<td>1.27-2.36</td>
<td>14</td>
<td>73</td>
</tr>
<tr>
<td>Deep vein thrombosis leg</td>
<td>1.84</td>
<td>1.21-2.82</td>
<td>9</td>
<td>115</td>
</tr>
<tr>
<td>Headache</td>
<td>0.93</td>
<td>0.87-0.99</td>
<td>25</td>
<td>39</td>
</tr>
<tr>
<td>Gynekological-/vasomotoric symptoms</td>
<td>1.08</td>
<td>1.06-1.10</td>
<td>64</td>
<td>16</td>
</tr>
<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 (Raloxifien)

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>
</tr>
</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>
</tr>
<tr>
<td>± LIN</td>
<td>3.76</td>
<td>3.89</td>
<td>1.03</td>
<td>0.81-1.33</td>
</tr>
<tr>
<td>+ LIN</td>
<td>9.83</td>
<td>9.61</td>
<td>0.98</td>
<td>0.58-1.63</td>
</tr>
<tr>
<td>± ADH</td>
<td>4.06</td>
<td>4.03</td>
<td>0.99</td>
<td>0.76-1.28</td>
</tr>
<tr>
<td>+ ADH</td>
<td>5.21</td>
<td>5.81</td>
<td>1.12</td>
<td>0.72-1.74</td>
</tr>
</tbody>
</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):

- 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)

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

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


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 assessment 2007
- CMJA: no update
- NICE: no update
- SIGN: no update
- Cochrane: Decision aids for risk communication update 2009
- DARE: no relevant references. 2010
- ASCO 2012: done
- National Institute of health (NIH): done
- San Antonio Breast Cancer Conference (SABCC 2013): done

References

National and international guidelines
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


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:

Further information:

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

References:


**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 (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 biopsy, the average upgrade rate is about 15%. The management of lobular neoplasia in excisional biopsies by the pathologist requires attention to the following points: 1) He should be aware of the risk of occult microinvasion and pay attention to the careful workup of the specimen. 2) In cases of pleomorphic LCIS attention must be paid to the margin status like in low-grade DCIS, to make sure that florid or pleomorphic LN has been completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.
References:


Statement: Indicator-/ precusor 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 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:

Further information:

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

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 tubular carcinoma. A 2- to 3-fold increase in the occurrence of ADH in the presence of FEA versus in their absence (P < .005) was observed. A finding of FEA on benign breast biopsy may indicate the presence of ADH, a more worrisome lesion (Boulos FI). FEA might be associated with noninvasive cancer but not with invasive cancer.

References:
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 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:*

Strategy after Diagnosis of Central Papilloma (17/25)

Further information:

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

References:

5. Rakha EA et al: Characterisation and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. *Int J Cancer*. 2010 Dec 2. [Epub ahead of print]


Radially Sclerosing Lesion (18/25)

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

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


IBIS.2

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 I, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F.
Ductal Carcinoma in Situ (DCIS)
Ductal Carcinoma in Situ
DCIS

- **Version 2002:** Gerber

- **Versions 2003–2015:**
  Audretsch / Blohmer / Brunnert / Costa / Fersis / Friedrich / Hanf / Junkermann / Lux / Maass / Möbus / Nitz / Oberhoff / Scharl / Solomayer / Souchon / Thill / Thomssen

- **Version 2016:**
  Friedrich / Kühn
# Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b A ++</td>
<td></td>
</tr>
<tr>
<td>4 C ++</td>
<td></td>
</tr>
<tr>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>5 D ++</td>
<td></td>
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<tr>
<td>3a C +/-</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>

- **Mammography**
  - Magnification view of microcalcification
  - Increase of detection rate of G1/G2 DCIS by full-field digital mammography (versus screen-film)
- **Stereotactic core needle / vacuum biopsy (VAB)**
  - Specimen radiography
  - Marker (Clip) left at biopsy site for location if lesion is completely removed
- **Assessment of extension**
  - MRI
  - Clinical examination
  - FNA / ductal lavage
  - Interdisciplinary board presentation
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

<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>Multivariate³ HR (95%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumpectomy</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>
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</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 Olcese, BS¹, Sujata Patil, PhD², Monica Morrow, MD, FACS¹, and Kimberly J. Van Zee, MS, MD, FACS¹

<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 Alone

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

Adjuvant treatment (radiotherapy, hormonal treatment) must be discussed with the patient individually. Disadvantages must be balanced against risk reduction.
Surgical Treatment for Histologically Proven DCIS I

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

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

- Histologically clear margins (R0)
- Multifocal DCIS: BCT if feasible
- Re-excision required for close margin ≤ 2 mm in paraffin section
- Mastectomy*
  - Large lesions confirmed by multiple biopsies; no clear margins after re-excision
- SNE*
  - BCT
  - Mastectomy
    - In case of DCIS in the male breast
- ALND

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

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

- Radiotherapy has no impact on survival  
  LOE 1a

- Radiotherapy reduces the risk of local (invasive and non invasive) recurrences by 50%  
  LOE 1a

- Avoidance of invasive recurrence is probably not associated with survival benefit  
  LOE 2b

- The absolute (individual) benefit of radiotherapy depends on the individual risk of local recurrence

- The number needed to treat (for any breast event) is 9 (over all risk groups)
## 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

<table>
<thead>
<tr>
<th>Modality</th>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>BCS</td>
<td>1a  A  +*</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>2b  B  - -</td>
</tr>
<tr>
<td>PBI</td>
<td>3a  D  --</td>
</tr>
<tr>
<td>Hypofractionated radiotherapy</td>
<td>2b  D  -/+**</td>
</tr>
<tr>
<td>Radiotherapy boost on the tumor bed</td>
<td>2b  D  --</td>
</tr>
<tr>
<td>Women younger than 45-50 years</td>
<td>2b  C  +/-</td>
</tr>
</tbody>
</table>

* 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 antihormonal treatment has no impact on survival  
  LOE 1a

- Postoperative antihormonal treatment may have a small effect on ipsilateral invasive recurrences  
  LOE 1a

- Antihormonal treatment for DCIS has an effect on contralateral invasive cancer and ipsilateral and contralateral DCIS  
  LOE 1a

- The number needed to treat for any breast event is 15  
  LOE 1a
Cochrane Analysis
Tamoxifen after DCIS (all/with Radiation)

Staley H, McCallum I, Bruce J.
Postoperative tamoxifen for ductal carcinoma in situ.
Cochrane Database Syst Rev. 2012 Oct 17;10:CD007847. doi:
10.1002/14651858.CD007847.pub2.

DCIS Postoperative Systemic Treatment

- Tamoxifen (only ER+)
- Aromatase inhibitor (only ER+) in postmenopausal women only
- Trastuzumab (only Her2+)

*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) (2/17)

No further information

No references
Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/17)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

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


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


- **Präparateradiographie**


> Klinische Untersuchung
> Feinnadelpunktion / duktale Lavage
> Interdisziplinäre Tumorboard-Präsentation
Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ (4-5/17)

No further information

Reference:

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD; JAMA Oncol. doi:10.1001/jamaoncol.2015.2510 Published online August 20, 2015.
Decreasing Recurrence Rates for Ductal Carcinoma In Situ: Analysis of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years (6/17)

No further information

Reference:

Preeti Subhedar, MD1, Cristina Olcese, BS1, Sujata Patil, PhD2, Monica Morrow, MD, FACS1, and Kimberly J. Van Zee, MS, MD, FACS1; Ann Surg Oncol (2015) 22:3273–3281
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 (8/17)

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 (Präparatradiographie)**

- Intraoperative Schnellschnittdiagnostik
- Interdisziplinäre Tumorboard-Präsentation
**Surgical Treatment for Histologically Proven DCIS II (9/17)**

*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 Local-/Locoregional Recurrence (10/17)

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
- Palpable + COX-2+p16+Ki-67+
- Palpable + 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)
ductal carcinoma in situ patients with and without irradiation. SABCS 2015. S5-04


DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom


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

Radiotherapy Statements (11/17)

Further information:
Alle Abstimmungen mit 100% Zustimmung

References:
See next slides
**DCIS Radiotherapy (12/17)**

Further information:

Alle Abstimmungen mit 100% Zustimmung.

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


11. 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)


Hypofraktionierte Radiotherapie


Boost-RT des Tumorbettes


Bei Patientinnen unter 45-50 Jahren
Cochrane Analysis – Radiation after Surgery (13/17)

No further information

No references
DCIS Postoperative Systemic Treatment - Statements (14/17)

No further information

References:

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

No further information

Reference:

H. Staley, I. McCallum, J. Bruce. The Breast 23 (2014) 546e551
DCIS Postoperative Systemic Treatment (16/17)

Further information:
Alle Abstimmungen mit 100% Zustimmung

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 (17/17)

Further information and references:

Abstimmung:
Lokalrezidiv des DCIS nach Tumorektomie nach Radiatio:

Einfache Mastektomie
++ 4/19;
+ 15/19

Einfache Mastektomie + SNB:
++ 3/22
+ 14/22
+/- 3/22
- 2/22
-- 0/22

Lokalrezidiv des DCIS nach Tumorektomie mit Radiotherapie

Therapieindikation wie bei primärer Erkrankung:
++ 10/21
+ 7/21
+/- 1/21
- 1/21
-- 2/21

Nach Radiatio
➢ Einfache Mastektomie

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


Keine Radiotherapie
Therapieindikation wie bei primär Erkrankung
Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Guidelines Breast
Version 2016.1

Breast Cancer Surgery
Oncological Aspects
Breast Cancer Surgery
Oncological Aspects

➢ **Versions 2002–2015:**
  Bauerfeind / Blohmer / Böhme / Costa / Fersis / Gerber / Hanf / Janni / Junkermann / Kaufmann / Kühn / Kümmel / Nitz / Rezai / Simon / Solomayer / Thill / Thomssen / Untch

➢ **Version 2016:**
  Brunnert / Solomayer
Surgery is only one sub-step out of multiple steps in breast cancer treatment. Thus, both a diagnostic and an oncological expertise are indispensable and a definite requirement.
Pretherapeutic Assessment

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

- Mammography  
  2b B ++

- Ultrasound (breast & axilla)  
  2b B ++

- Minimal invasive biopsy*  
  1c A +

- MRI**  
  1c B +/-

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

** No significant reduction of re-excision rate.

The possibility of MRI guided biopsy is the precondition of breast MRI (e.g. dense breast tissue and invasive lobular cancer, suspicion of multifocal or multicentric disease)
Perioperative Staging

- 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
  - Oxford / AGO LoE / GR:
    - History and physical examination: 5 D ++
    - Chest X-ray: 5 D +
    - Liver ultrasound: 5 D +
    - CT-scan: 5 D +
    - Bone-scan: 5 D +
    - FDG-PET or FDG-PET / CT: 4 C -
    - Whole body MRI: 4 C -
Evidence of Surgical Procedure

- Survival rates after lumpectomy + XRT are equivalent to those after (modified) radical mastectomy  
  1a A

- Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy  
  1b A

- Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy  
  2b B

- Conservation of the NAC (nipple areola complex) is an adequate surgical procedure in tumors of the periphery of the gland and after tumor-free section of retroareolar tissue  
  4b C
# Breast Conservation: Surgical Technical Aspects

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

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

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

Oxford / AGO
LoE / GR

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<td>3</td>
<td>A</td>
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<tr>
<td>1b^a</td>
<td>B</td>
<td>+</td>
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</tbody>
</table>

* Study participation recommended
Surgical Treatment of Axillary Lymph Nodes post NACT (Neoadjuvant Chemotherapy) (N+)

- NACT (+/- Anti-HER 2 therapy) down-stages axillary nodes in 20->50%
- Possibility of avoiding ALND after NACT
- Reducing SLNB FNR by removal of >2sn and dual agent SN-mapping (radiocolloid + blue dye)
- Consideration of IHC staining in the SN
- Clip localization of positive nodes pre NACT
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>Oxford / AGO</th>
<th>LoE / GR</th>
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<td>B</td>
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</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>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>nihil</td>
<td>3b</td>
<td>B</td>
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<td></td>
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<td></td>
<td>Re-SLNB alone ALND</td>
<td>3b</td>
<td>B</td>
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<td>3b</td>
<td>B</td>
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<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>Re-SLNB alone ALND</td>
<td>2b</td>
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<td>(not analog ACOSOG Z0011)</td>
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<td></td>
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<td></td>
<td>Axilla XRT</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>cN0</td>
<td>not done</td>
<td>ycN0</td>
<td>SLNB alone ALND</td>
<td>2b</td>
<td>B</td>
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<td></td>
<td></td>
<td></td>
<td>ALND</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA + clip placement)</td>
<td>ycN0</td>
<td>SLNB alone* ALND</td>
<td>2b</td>
<td>B</td>
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<td>ycN0</td>
<td></td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ycN0</td>
<td></td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

* Analogue ACOSOGZ1071
# Sentinel Lymph Node Biopsy (SLNB): Indications I

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>A</th>
<th>B</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically (cN0) / sonographically neg. axilla</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Add. FNA/CNB of LN (clinical/sonogr. suspicious + Clip localization if NACT) in order to enable SLNB</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>T 1-2</td>
<td>2b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>T 3, 4a-c</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Multifocal / multicentric lesions</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>DCIS</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>DCIS in male</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>BCT</td>
<td>3b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In the elderly</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
Sentinel Lymph Node Excision (SNE): Indications II

- During pregnancy and / or breast feeding (no blue dye)
- After previous tumor excision
- Previous major breast surgery (e.g. reduction mammoplasty, mastectomy)
- Ipsilateral breast recurrence after prior BCS and prior SNE
- SN in the mammarian internal chain
- After axillary surgery
- Prophylactic bilateral / contralateral mastectomy
- Inflammatory breast cancer

Oxford / AGO LoE / GR

- During pregnancy and / or breast feeding (no blue dye): 3 C +
- After previous tumor excision: 2b B +
- Previous major breast surgery (e.g. reduction mammoplasty, mastectomy): 3b C +/-
- Ipsilateral breast recurrence after prior BCS and prior SNE: 4 D +/-*
- SN in the mammarian internal chain: 2b B -
- After axillary surgery: 3b B +/-*
- Prophylactic bilateral / contralateral mastectomy: 3b B - -
- Inflammatory breast cancer: 3b C +/-

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

- **99mTc Kolloid**
- Blue dye
- Methylene blue
- Indocyanin green (ICG)*
- SPIO#

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>4 D -</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>

# SPIO: Superparamagnetic Iron Oxide

* Study participation recommended
### Procedure after Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marking of tumor in a timely manner</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Surgery</td>
<td>2b C ++</td>
</tr>
<tr>
<td>Microscopically clear margins</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Tumor resection in the new margins</td>
<td>3b C +</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1b</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start adjuvant systemic therapy and RT as soon as possible (a.s.a.p.) after surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Start of adjuvant chemotherapy after surgery a.s.a.p., and prior to RT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Without cytotoxic therapy:**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>B</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start irradiation 6-8 weeks after surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Start endocrine therapy after surgery and a.s.a.p.</strong></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>3b</th>
<th>C</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen concurrent with radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AI concurrent with radiotherapy</strong></td>
<td></td>
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</tr>
</tbody>
</table>
Further information and references:

Update Januar 2015
Screened consensus conference:
Cochrane library:
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

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

No 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 treatment (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

- **Versions 2002–2015:** Audretsch / Bauerfeind / Blohmer / Brunnert / Dall / Fersis / Hanf / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Thomssen

- **Version 2016:** Gerber / Rezai
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
- Local flap techniques
- Partial mastectomy with tissue transfer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford/AGO LoE/GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor adapted reduction mammaplasty</td>
<td>2a B +</td>
</tr>
<tr>
<td>Local flap techniques</td>
<td>2a B +</td>
</tr>
<tr>
<td>Partial mastectomy with tissue transfer</td>
<td>3b B +/-</td>
</tr>
</tbody>
</table>
Patient wishes to undergo breast reconstruction
N.B.: Habitus, breast volume, wishes

No postmastectomy radiotherapy

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

Postmastectomy radiotherapy indicated

- Mastectomy
  - → Radiotherapy
  - → Delayed autologous reconstruction

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

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

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

- Delayed prothesis reconstruction
  - N.B.: Increased complication rate
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 2a B +
- Autologous tissue reconstruction 2a B +
- Pedicled tissue reconstruction 2a B +
- Free tissue reconstruction 2a B +
- Autologous tissue combined with implants 3a C +

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

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

- **Delayed BR**
  - Disadvantage: loss of skin envelope

- „Delayed-immediate“ BR

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
<th>Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>

www.ago-online.de
Timing of Implant Based Reconstruction and Radiotherapy

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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPLANT RECONSTRUCTION (IR)</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>IR without radiotherapy (RT)</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>IR prior to RT / following PBRT (higher complication rate)</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>IR following MX and RT</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>IR following Mx for local relapse after BCT</td>
<td>2a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Periop. antibiotic therapy (at least 48 h)</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

*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 to fix the muscle  
  - Oxford / AGO LoE / GR: 2b B +#

* LDF = Latissimus dorsi flap

# Participation in register studies recommended
Lipotransfer

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

- Lipotransfer after breast-conserving therapy
  - Oxford / AGO LoE / GR: 4 D +

- 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) 3b C +
- Delayed TRAM in risk patients 3a B +
- Ipsilateral pedicled TRAM 3b A +

Radiotherapy:

- BR following RT 2 a B +
- BR prior to RT (more fibrosis, more wound healing problems, more liponecrosis) 2a B +/-

Oxford / AGO LoE / GR
## Free Tissue Transfer

### Free tissue transfer
- DIEP-flap
- Free TRAM-flap
- SIEA-flap
- SGAP- / IGAP-flap
- 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 rate of re-operations and total failure rate
- Pre-reconstruction RT increases rate of vascular complications
- No higher patient satisfaction than with pedicled TRAM in multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Oxford</th>
<th>AGO</th>
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<tbody>
<tr>
<td>Free Tissue Transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>B</td>
</tr>
<tr>
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<td>3a</td>
<td>C</td>
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<td></td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>C</td>
</tr>
</tbody>
</table>
Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used

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

Perforator flaps appear to have a higher risk for fat necrosis than free or pedicled TRAM

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

Oxford / AGO
LoE / GR
2b C +
3b C +
5 D -
5 C +/-
Skin/Nipple Sparing Mastectomy (SSM/NSM) and Reconstruction

- **Skin sparing mastectomy (SSM/NSM)**
  - Safe (same recurrence rate as MX) 2b B ++
  - Higher QoL for patients 2b B ++
  - NAC can be preserved under special conditions 2b B ++
    - Feasible after mastopexy / reduction mammoplasty
  - 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 2b B +
Risk Reducing Bilateral Mastectomy in Healthy Women (RRBM)

- RRBM reduces breast cancer incidence
- RRBM in deleterious BRCA1/2 mutation
- RRBM in high risk (i.e. lifetime risk >=30% or heterozygote risk >=20%) but index case negative for BRCA1/2 mutations
- High risk and no BRCA counselling in specialized centre *
- Non-directive counselling prior to RRBM
- RRBM should be considered with other prophylactic surgical options incl. bilateral salpingoophorectomy (BSO)
- Further need for education of physicians regarding possibilities and advantages of RRBM

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Guideline</th>
<th>LoE</th>
<th>AGO</th>
<th>Oxford</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>RRBM reduces breast cancer incidence</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>RRBM in deleterious BRCA1/2 mutation</td>
<td>2a</td>
<td>B</td>
<td>+*</td>
<td></td>
</tr>
<tr>
<td>RRBM in high risk (i.e. lifetime risk &gt;=30% or heterozygote risk &gt;=20%)</td>
<td>3a</td>
<td>C</td>
<td>+/-*</td>
<td></td>
</tr>
<tr>
<td>High risk and no BRCA counselling in specialized centre *</td>
<td>5</td>
<td>D</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>Non-directive counselling prior to RRBM</td>
<td>2b</td>
<td>B</td>
<td>++*</td>
<td></td>
</tr>
<tr>
<td>RRBM should be considered with other prophylactic surgical options</td>
<td>2a</td>
<td>A</td>
<td>++*</td>
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<tr>
<td>incl. bilateral salpingoophorectomy (BSO)</td>
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</tr>
<tr>
<td>Further need for education of physicians regarding possibilities and</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>advantages of RRBM</td>
<td></td>
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</tr>
</tbody>
</table>

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

Screened data bases:

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):
Definition of oncoplastic surgery (3/18):

Further information:

AGO Voting for giving a new definition 45/0

References:

Oncoplastic breast conserving surgery (4/18)

Further information:

AGO Voting for this slide and content 45/0

References:

Algorithm of Breast Reconstruction (5/18)

Further information:

AGO Voting for this slide and content 45/0

References:

Further information:

Voting for this new slide and content 45/0

References:

Postmastectomy Reconstruction (7/18)

Further information:

Voting for this new slide and content 45/0

References:

Timing of Reconstruction (8/18)

Further information:

No voting this year

References:

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

Further information:

AGO voting for implant reconstruction before radiation:

References:

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

*Further information:*

Voting for new headline 45/0

*References:*

Lipotransfer (11/18)

Further information:

AGO voting for changing the wording from “lipofilling” to “Lipotransfer”: 45/0
Voting for new wording statement 1: 45/0

Reference:

Postmastectomy (pedicled) Reconstruction (12/18)

Further information:

Voting for whole content with one consent

References:

5. Garvey PB$^1$, Clemens MW, Hoy AE, Smith B, Zhang H, Kronowitz SJ, Butler CE. Muscle-sparing TRAM flap does not protect breast reconstruction from postmastectomy radiation damage compared with the DIEP flap. Plast Reconstr Surg. 2014 Feb;133(2):223-33
Free Tissue Transfer (13/18)

Further information:

Voting:
For Free TRAM-flap 11 +; 12 +/-
DIEP-flap + with one consent

References:


Pedicled vs. Free Tissue Transfer (14/18)

Further information:

No voting this year

Reference:

Flap-Implant Combination (15/18)

Further information:

No voting this year

References:

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

Further information:

No voting this year

References:

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

Further information:

No voting this year
Please see chapter breast Cancer Risk and Prevention

References:

Types of Risk Reducing Mastectomy (18/18)

Further information:

No voting this year
Please see chapter breast Cancer Risk and Prevention

References:


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

- **Versions 2002–2015:**
  Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber / Göring / Harbeck / Huober / Jackisch / Lisboa / Lück / Maass / von Minckwitz / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2016:**
  Jackisch / Schneeweiss
Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1
GR: A
AGO: ++

Endocrine responsiveness:
Immunohistochemistry (ER and / or PgR)

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

Status unknown: endocrine responsive
Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Assessment of menopausal status

- Menstruation history  
- FSH, E2

Oxford / AGO
LoE / GR

+ 
++
Adjuvant Endocrine Therapy

Standard therapy in endocrine responsive tumors:

- Endocrine therapy  
  1a A ++

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

- Endocrine responsive & doubtful:
  - Endocrine therapy
  - Endocrine therapy sequentially after CT
- Non-responsive:
  - No endocrine therapy

Oxford / AGO LoE / GR

1a A ++
2b C ++
1a A ++
General Principles in Adjuvant Endocrine Therapy

AGO ++

- Standard treatment duration 5 years
- Treatment up to 10 years may be considered based on the individual risk of relapse (e.g., N+ status at presentation)
- Duration, choice & sequence of AI or Tam mainly rely on menopausal status and side effects
- Switch to another endocrine treatment (Tam or AI) is better than to stop
- AI as first treatment preferably in postmenopausal patients at high risk and lobular cancers
- So far no evidence for AI > 5 yrs
**Premenopausal Patients**  
**Adjuvant Endocrine Therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen* 5-10 yrs.</td>
<td>1a A</td>
<td>++</td>
</tr>
<tr>
<td>GnRHa alone</td>
<td>1a B</td>
<td>+</td>
</tr>
<tr>
<td>(only if relevant contraindications for Tam)</td>
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<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>#OFS (ovarian function suppression) 5 yrs. + TAM 5 yrs.</td>
<td>1b B</td>
<td>+/-</td>
</tr>
<tr>
<td>#OFS 5 yrs. + AI 5 yrs.</td>
<td>1b B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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

#### Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI alone</td>
<td>1c A - -</td>
</tr>
<tr>
<td>AI after GnRHa (induced amenorrhea)</td>
<td>5 D - -</td>
</tr>
<tr>
<td>Upfront AI in patients with chemotherapy-induced amenorrhea (CIA, TIA)</td>
<td>4 C - -</td>
</tr>
<tr>
<td>EAT in perimenopausal pts. with validated postmenopausal status after 5 yrs. of Tam</td>
<td>2b B +</td>
</tr>
<tr>
<td>Reduction of POF* caused by adjuvant chemotherapy</td>
<td>1b B +/-</td>
</tr>
</tbody>
</table>

*POF: Premature ovarian failure*
Postmenopausal Patients
Adjuvant Endocrine Therapy

- **AI for 5 yrs.**
  - Preference in lobular inv. cancers
- **Sequential therapy for 5 -10 yrs.**
  - Tam followed by AI (2-5 yrs.)*
  - AI (2-5 yrs.)* followed by Tam
    Preference in N+
- Tamoxifen 20 mg/d for 5-10 yrs.

*Duration of AI ≤ 5 yrs.

---

Oxford / AGO
LoE / GR

1a A +
2b B ++
++
1a A
1b C
1a A ++
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

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

Impairment of CT – effect cannot be excluded!

- Fertility preservation counselling
- Fertility preservation with assisted reproduction therapy (further information www.fertiprotect.de)
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.
Contraceptive Options for Women after Diagnosis of Breast Cancer

- **Barrier methods**
  - Oxford / AGO LoE / GR: 5 D +

- Sterilization (tubal ligation / vasectomy)
  - Oxford / AGO LoE / GR: 5 D +

- Non-hormonal intrauterine devices (IUDs)
  - Oxford / AGO LoE / GR: 3b D +

- Levonorgestrel-releasing IUDs
  - Removal in newly diagnosed patients
    - Oxford / AGO LoE / GR: 4 D +/-

- **Timing methods**
  - Oxford / AGO LoE / GR: 5 D -

- Injectable progestin-only contraceptives
  - Oxford / AGO LoE / GR: 5 D -

- Progestin-only oral contraceptives
  - Oxford / AGO LoE / GR: 5 D -

- Combined oral contraceptives
  - Oxford / AGO LoE / GR: 5 D -
Emergency Contraception after Diagnosis of Breast Cancer

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

Vorteil GnRHa / Vorteil Kontrolle

nach Del Mastro et al. Cancer Treat Rev 2014
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)

- Tamoxifen 20 mg/day + OFS* (n = 1328)
- Exemestane 25 mg/day + OFS* (n = 1332)
- Tamoxifen 20 mg/day

Joint Analysis

- Tamoxifen + OFS* (n = 2344)
- Exemestane + OFS* (n = 2346)

*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

# Aromatase Inhibitors in Adjuvant Therapy

## Overview over Published Trials: Upfront and Extended Therapy

<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 HR 0.79, p=0.002; TTDR HR 0.85, p=0.02</td>
<td>HR 0.87 p=0.4</td>
<td>SAE T&gt;A, gyn AE T&gt;A, VE T&gt;A, SE A&gt;T</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>upfront 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, gyn AE T&gt;L, TE T&gt;L, CE L&gt;T, SE L&gt;T</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, DFS HR 0.95</td>
<td>ns</td>
<td>Osteoporosis A&gt;E, El. liver enzymes E&gt;A, Hyperlipidaemia A&gt;E</td>
<td>Randomization for Celecoxib cancelled</td>
</tr>
</tbody>
</table>

### Extended Therapy

<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>MA 17</td>
<td>Goss 2005</td>
<td>L</td>
<td>extended after 5y T vs P</td>
<td>5170</td>
<td>30</td>
<td>DFS HR 0.58, p=0.01; TTR HR 0.60, p=0.01; CBC HR 0.63, p=0.13</td>
<td>HR 0.61 in N+, p=0.04</td>
<td>CE L=P, SE L&gt;P</td>
<td>QoL↓ (Whelan 2005) Lipids → (Wasan 2005)</td>
</tr>
<tr>
<td>ABCG6a</td>
<td>Jakesz 2007</td>
<td>A</td>
<td>extended after 5y T vs Nil</td>
<td>856</td>
<td>62</td>
<td>DFS HR 0.642 p=0.031</td>
<td>ns</td>
<td>CE E=P, SE L&gt;P</td>
<td></td>
</tr>
<tr>
<td>NSABP-B33</td>
<td>Mamounas 2008</td>
<td>E</td>
<td>Extended after 5y T vs P</td>
<td>1598</td>
<td>30</td>
<td>DFS HR 0.68 p=0.07, RFS HR 0.44 p=0.004</td>
<td>ns</td>
<td>SE E=P after 6 Mo</td>
<td>Grad 3 AE E&gt;P 9% vs 3%, p=0.03, Profit from E particular in N+</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
## Aromatase Inhibitors in Adjuvant Therapy
### Overview over Published Trials: Switching/Sequential trials

<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>IES</td>
<td>Bliss JM</td>
<td>E</td>
<td>switch after 2-3y T vs T</td>
<td>4599</td>
<td>91</td>
<td>DFS HR 0.76, ITT p&lt;0.01</td>
<td>DFS HR 0.75, ER+/u</td>
<td></td>
<td>HR, 0.86; 95% CI, 0.75 to 0.99; P = .04. gyn AE T&gt;A TE T&gt;E SE E&gt;T diarrhea E&gt;T</td>
</tr>
<tr>
<td>ITA</td>
<td>Boccardo 2006</td>
<td>A</td>
<td>switch after 2-3y T vs T</td>
<td>448</td>
<td>64</td>
<td>EFS HR 0.57, p&lt;0.01</td>
<td>DFS HR 0.56, p=0.01</td>
<td></td>
<td>ns SAE T&gt;A</td>
</tr>
<tr>
<td>ABCSG -08</td>
<td>Jakesz 2005</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>3224</td>
<td>28</td>
<td>DFS HR 0.59, p&lt;0.01</td>
<td>TTR HR 0.60, p&lt;0.01</td>
<td>HR TTR 0.61, p=0.01</td>
<td>ns TE T&gt;A SE A&gt;T</td>
</tr>
<tr>
<td>ARNO 95</td>
<td>Kaufmann 2007</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>979</td>
<td>30</td>
<td>DFS HR 0.66, p=0.049</td>
<td>HR 0.53, p=0.045</td>
<td></td>
<td>SAE T&gt;A 30.8 vs 22.7 %</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Regan et al 2011</td>
<td>L</td>
<td>switch after 2y T vs. Let</td>
<td>1548</td>
<td>97</td>
<td>disease-free survival;</td>
<td>89.9%, 88.7%, 88.1%</td>
<td>ns</td>
<td>SE L=T VE L = T</td>
</tr>
<tr>
<td>TEAM</td>
<td>Van de Velde 2011</td>
<td>E</td>
<td>TEAM: E alone vs Tam switch after 2 – 3 y to E</td>
<td>4868</td>
<td>60</td>
<td>hazard ratio 0.97, 95% CI 0.88-1.08; p=0.60</td>
<td>n.a.</td>
<td>DVT; endometrial &gt; switch Musculoskeletale problems hyperlipidaemia &gt; E mono</td>
<td></td>
</tr>
<tr>
<td>N-SAS BC03</td>
<td>Aus Japan 2010</td>
<td>A</td>
<td>Tam 5 y vs Tam→ A switch after 1 – 4 y Tam</td>
<td>706</td>
<td>42</td>
<td>DFS: 0.69 P = 0.14 RFS 0.54 P = 0.06</td>
<td>n.a.</td>
<td>dito</td>
<td></td>
</tr>
</tbody>
</table>

**Meta-analysis**

| ARNO95 ABSCG8 ITA | Jonat 2006 | A | switch (2-3y T) | 4006 | DFS HR 0.59, p<0.01 | HR 0.71, p=0.04 | with heterogeneity |

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

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Details</th>
</tr>
</thead>
</table>
| FSH (follicle stimulating hormone) plus estradiol | • Serum level on cycle day 2–3  
• Variation between cycles possible  
• High FSH value is associated with poor response to ovarian stimulation |
| Anti Müllerian Hormone (AMH)              | • No specific timing for the test  
• Stable value within and between menstrual cycles  
• Low AMH value is associated with poor response to ovarian stimulation |
| Antral follicle count (AFC)               | • Number of visible follicles (2–10 mm) during transvaginal ultrasound  
• Performed on cycle days 2–5  
• Number of antral follicles correlates with ovarian response to stimulation |

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.
<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)</td>
<td>0.92 (0.77-1.09)</td>
<td>0.97 (0.84-1.15)</td>
</tr>
<tr>
<td><strong>Years 10+</strong></td>
<td>0.75 (0.63-0.90)</td>
<td>0.75 (0.63-0.90)</td>
<td>0.75 (0.65-0.86)</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.07</td>
<td>0.002</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>All years</strong></td>
<td>0.88 (0.74-1.03)</td>
<td>0.83 (0.73-0.86)</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td><strong>p</strong></td>
<td>0.1</td>
<td>0.004</td>
<td>0.001</td>
</tr>
</tbody>
</table>

nach Grey et al ASCO 2013  
*J Clin Oncol 31, 2013 (suppl. Abstr 5)*
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients (2/21)

No further information

No references
Assessment of Steroid Hormone Receptor Status (3/21)

No further information

References:

Statement 1
Adjuvant Endocrine Therapy – Assessment of Menopausal Status (4/21)

No further information

References:

Adjuvant Endocrine Therapy (5/21)

No further information

References:


Adjuvant Endocrine Therapy (6/21)

No further information

References:

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

Further information:

Voting: 18/7

References:

**Premenopausal Patients - Adjuvant endocrine therapy (8/21)**

*Further information and references:*

**Tamoxifen** 5-10 yrs.  1a  A  ++  Voting: 100% acceptance


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


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

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

OFS 5 yrs. + AI 5 yrs. 1b B +/- Voting: 100% acceptance


**Premenopausal Patients – Adjuvant Endocrine Therapy (9/21)**

*Further information and references:*

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


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

5. Goss PE et al: Outcomes of women who where premenopausal at diagnosis of early stage breast cancer. Cancer Res 69(Suppl.1);2009:487s(#13)

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

**EAT in perimenopausal pts. with validated postmenopausal status after 5 yrs. of Tam** 2b B + Voting: 100% acceptance

Postmenopausal patients – adjuvant endocrine therapy (10/21)

Further information and references:

**AI for 5 yrs.**

1a A +  Voting: 100% acceptance

**Preference in lobular inv. Cancers**

2b B +  Voting: 100% acceptance

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

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

+++ 

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

**Tamoxifen 20 mg/d for 5-10 yrs.** 1a A ++ Voting: 100% acceptance

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

Further information and references:

Ovarian Function Protection

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


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

Testing ovarian reserve (12/21)

No further information

References:


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

No further information

References:

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

No further information

No references
Ovarian Function Preservation - Comparison of Randomized Trials (15/21)

No further information

No references
Metaanalysis of GnRH for Prevention of Premature Ovarian Failure (16/21)

No further information

No references
TEXT/SOFT Joint Analysis (17/21)

No further information

No references
Aromatase inhibitors in Adjuvant Therapy (18/21)

No further information

No references
Aromatase inhibitors in Adjuvant Therapy – Overview over Published Trials (19/21)

No further information

No references
Assessment of Ovarian Reserve (20/21)

No further information

No references
10 Yrs versus 5 yrs Breast Cancer Mortality in ER+ (21/21)

No further information

No references
Adjuvant Cytotoxic and Targeted Therapy
Adjuvant Cytotoxic and Targeted Therapy

- **Version 2002:** Möbus / Nitz

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

- **Version 2016:** Möbus / von Minckwitz
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”
- Con conventionally dosed AT-based chemotherapy ++
- Dose dense & escalated in case of high tumor burden +
- Followed by endocrine therapy ++

HER2+
- Trastuzumab plus ++
  - Sequential A/T-based regimen with concurrent T + H ++
  - Anthracycline-free, carboplatinum-containing regimen +
  - Anthracycline-free, taxane regimen for low tumor burden +
  - Dose dense & escalated in case of high tumor burden +

TNBC
- Conventionally dosed AT-based chemotherapy ++
- Dose dense & escalated +
- Neoadjuvant platinum containing chemotherapy +
Adjuvant Chemotherapy without Trastuzumab: Overview

- Anthracycline / taxane based chemotherapy
  - If anthracyclines cannot be given
    - Docetaxel plus cyclophosphamide
    - Paclitaxel mono weekly
    - CMF
  - Dose-dense in case of high tumor burden

Oxford / AGO LoE / GR

- Anthracycline / taxane based chemotherapy
  - 1a A ++
  - If anthracyclines cannot be given
    - Docetaxel plus cyclophosphamide
      - 1b B +
    - Paclitaxel mono weekly
      - 1b B +/-
    - CMF
      - 1a A +/-
  - Dose-dense in case of high tumor burden
    - 1a A ++
Recommended Regimens for Adjuvant Chemotherapy

**Anthracycline / taxane based regimen**

- **EC → P**<sub>w</sub>  
  E<sub>90</sub>C q3w x 4 → P<sub>80</sub> qw1 x 12  
  1b  B  ++

- **AC → P**<sub>w</sub>  
  A<sub>60</sub>C q3w x 4 → P<sub>80</sub> qw1 x 12  
  1b  A  ++

- **AC → D**  
  A<sub>60</sub>C q3w x 4 → D<sub>100</sub> qw3 x 4  
  1b  A  ++

- **EC → D**  
  E<sub>90</sub>C q3w x 4 → D<sub>100</sub> qw3 x 4  
  1b  B  ++

- **DAC**  
  D<sub>75</sub>A<sub>50</sub>C q3w x 6  
  1b  A  ++

**Anthracycline-free regimen**

- **DC**  
  D<sub>75</sub> C<sub>600</sub> x4  
  1b  B  +

- **Pac mono**  
  P<sub>80</sub> q1w x 12  
  1b  B  +/-

- **CMF**  
  1a  A  +/-

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

Dose-dense regimen

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

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

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

* Extrapolated from doxorubicin trials
# Adjuvant Chemotherapy

## Other Drugs

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

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

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
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<tbody>
<tr>
<td>1b</td>
<td>B</td>
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<tr>
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<td>++</td>
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<tr>
<td>1b</td>
<td>A</td>
<td>-</td>
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</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant Trastuzumab
Cardiac Monitoring for CHF

Oxford LoE: 5  GR: D  AGO: ++

Before start of trastuzumab
- History, physical examination (edema, hepatomegaly)
- Echocardiography (alternative to MUGA)

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
- With P q1w 12 x without A in pT < 3 cm, pN0
- With docetaxel and carboplatin
- With anthracyclines
- With taxanes dose-dense

Radiotherapy concurrent with Trastuzumab

Oxford / AGO LoE / GR

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

* Study participation recommended
Adjuvant Therapy with Other Targeted Agents

- **Lapatinib**
  - (delayed adjuvant treatment)
  - Oxford / AGO LoE / GR: 1\textsuperscript{b}\textsuperscript{a} B -

- **Lapatinib + Trastuzumab**
  - Oxford / AGO LoE / GR: 1\textsuperscript{b}\textsuperscript{a} B -

- **Pertuzumab**
  - Oxford / AGO LoE / GR: 5 D -

- **Bevacizumab**
  - Oxford / AGO LoE / GR: 1b B --
Adjuvant Cytotoxic and Targeted Therapy (2/12)

No further information

No references
Subtype-specific general systemic strategies (3/12)

No further information:

References:

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

**Further information and references:**

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

Vote result of the AGO recommendation: 100%


**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%


Recommended Regimens for Adjuvant Chemotherapy (5/12)

Further information and references:

Statement: Anthracycline/ taxane based regimen
*EC → Pw E90C q3w x 4 → P80 qw1 x 12 (1b B ++)
Vote result of the AGO recommendation: 100%


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 (6/12)

Further information and references:

Statement: Dose-dense regimen
*EC q3w Pac q1w x 12 (1b B++)
AC q3w / Pac q1w x 12 (1b A++)
Vote result of the AGO recommendation: 100%


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 (7/12)**

**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-Fuorouracile added to EC/AC (1b A --)**

Vote result of the AGO recommendation: 100%

Adjuvant treatment with trastuzumab I (8/12)

Further information and references:

Statements: Node-positive and node-negative disease (1a A++)
Vote result of the AGO recommendation: 100%


Statements: >10 mm/> 5-10 mm/ <= 5mm (1a A ++ / 2b B + / 2b B +/-)
Adjuvant treatment with Trastuzumab II (9/12)

Further information and references:

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


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 – Cardia monitoring for CHF (10/12)

Further information and references:

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

**Adjuvant treatment with trastuzumab: Schedules (11/12)**

**Further information and references:**

**Statement:** with paclitaxel/docetaxel after AC/EC (1b A ++)
Vote result of the AGO recommendation: 100%


**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 8.

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

See references slide 8.

Statement: radiotherapy concurrent with trastuzumab (2b B +)
Vote result of the AGO recommendation: 100%

**Adjuvant Therapy with Other Agents (12/12)**

**Further information and references:**

**Statement:** with Lapatinib (1b° B -)

*Delayed adjuvant treatment (1b B -)*

Vote result of the AGO recommendation: 100%


**Statement:** with Lapatinib + Trastuzumab (1b° 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%


Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Version 2002:**
  Costa

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

- **Version 2016:**
  Liedtke / Untch
Subtype-specific
General Systemic Strategies

If chemotherapy is indicated consider systemic treatment before surgery (neoadjuvant)

HR+/HER2- and “low risk”:
- Endocrine therapy without chemotherapy

HR+/HER2- and “high risk”
-Conventionally dosed AT-based chemotherapy
- Dose dense & escalated in case of high tumor burden
- Followed by endocrine therapy

HER2+
- Trastuzumab plus
  - Sequential A/T-based regimen with concurrent T + H
  - Anthracycline-free, carboplatinum-containing regimen
  - Anthracycline-free, taxane regimen for low tumor burden
  - Dose dense & escalated in case of high tumor burden

TNBC
- Conventionally dosed AT-based chemotherapy
- Dose dense & escalated
- Neoadjuvant platinum containing chemotherapy
Neoadjuvant Systemic Chemotherapy
Clinical Benefit

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

* Study participation recommended
Neoadjuvant Systemic Chemotherapy

Indications

- Inflammatory breast cancer
- Inoperable breast cancer
- Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation
- If similar postoperative adjuvant chemotherapy is indicated

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>B</th>
<th>++</th>
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<tr>
<td></td>
<td>1c</td>
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<td>B</td>
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<tr>
<td></td>
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### Neoadjuvant Systemic Chemotherapy Response Prediction I

<table>
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<tr>
<th>Factor</th>
<th>CTS</th>
<th>LoE&lt;sub&gt;Ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
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<tr>
<td>Young age</td>
<td>B</td>
<td>1a</td>
<td>A</td>
<td>+</td>
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<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>
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## Neoadjuvant Systemic Therapy Response Prediction II

<table>
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<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
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<tr>
<td>Multigene signatures</td>
<td>III</td>
<td>C</td>
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<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>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
  
- In TNBC Nab-Paclitaxel qw instead of Paclitaxel qw

*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></td>
<td>SABCS 2015</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 15mg/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></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>
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<td></td>
<td>BCRT 2014</td>
<td></td>
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</tbody>
</table>
### Neoadjuvant Systemic Chemotherapy

#### Recommended Methods of Monitoring of Response

- Breast ultrasound: 2b B ++
- Palpation: 2b B ++
- Mammography: 2b B ++
- MRI: 2b B +
- PET(-CT)*: 2b B +/-
- Clip tumor region: 5 D ++

* Study participation recommended
Neoadjuvant Targeted Therapy in HER2 Positive Tumors

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

Oxford / AGO LoE / GR

1b A ++

2b C +
Neoadjuvant Systemic Therapy
Procedures in Case of No Early Response

In case of no change:

- Completion of NST, followed by surgery  
  - 2b C ++
- Continuation of NST with non cross-resistant regimen
  - AC or EC x 4 → D x 4 or Pw x 12  
    - 2b B ++
  - DAC x 2 → NX x 4  
    - 1b B +

In case of progressive disease:

- Stop of NST and surgery or radiotherapy  
  - 4 D ++*
- Additional adjuvant chemotherapy with non cross-resistant regimen  
  - 4 D +/-*

* Study participation recommended
Local / Regional Procedure after Neoadjuvant Therapy

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark previous tumor region</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Surgery</td>
<td>2b C ++</td>
</tr>
<tr>
<td>Microscopically clear margins</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Tumor resection according to imaging result</td>
<td>3b C +</td>
</tr>
</tbody>
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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>
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<td>2b</td>
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### Further surgical procedures depending on SLNB status

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<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>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
<td>1a A +</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>nihil</td>
<td>3 B +/-</td>
</tr>
<tr>
<td></td>
<td>(analog ACOSOG Z0011)</td>
<td></td>
<td>Re-SLNB alone ALND</td>
<td></td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn)</td>
<td>ycN0</td>
<td>Re-SLNB alone ALND Axilla XRT</td>
<td>2b 2b B +</td>
</tr>
<tr>
<td></td>
<td>(not analog ACOSOG Z0011)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN0</td>
<td>not done</td>
<td>ycN0</td>
<td>SLNB alone ALND</td>
<td>2b 2b B +/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA + clip placement)</td>
<td>ycN0</td>
<td>SLNB alone* ALND ALND</td>
<td>2b 2b B +/-</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>
# 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  
      - **Oxford / AGO LoE / GR**: +/-

- 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**

<table>
<thead>
<tr>
<th>Level</th>
<th>Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>
Adjuvant Systemic Therapy after Neoadjuvant Systemic Treatment

- Endocrine treatment in endocrine responsive disease
  
  1a A ++

- Complete trastuzumab treatment for 1 year in HER2-positive disease
  
  2b B ++

- Complete pertuzumab treatment for 1 year in HER2-positive disease
  
  3 C -

- If insufficient response in case of non-pCR (invasive residual tumor in the breast and / or axillary nodes) after adequate NACT (antracyclines, taxanes, 18 weeks)
  
  - Capecitabine adjuvant
    
    1b\textsuperscript{a} B +/-
  
  - Further chemotherapy
    
    3 C -
  
  - Experimental therapies in clinical trials
    
    5 D +
Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

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

- **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 Prediction 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
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: 3/18/8/0/0 (2016)

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: 0/4/5/0/0 (2016)

**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**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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


**DAC x 2 → NX x 4**
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


**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
Preliminary Note

- The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between experts of the AGO and DEGRO.

- For technical details of radiotherapy we recommend to refer to the corresponding updated DEGRO practical guidelines 2014.

- If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue colour.
### Guidelines and Opinions

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

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

<table>
<thead>
<tr>
<th>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).</th>
</tr>
</thead>
</table>

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

With regard 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

LoE 1b B AGO ++

- Hypofractionated RT with sequential boost or conventional RT with integrated or sequential boost
- Low risk*: hypofractionated RT without boost (15-16 fractions)
- High risk: RT as for <50 years
- Individual counseling including omission of radiotherapy according to individual risk after geriatric assessment
- If radiotherapy of the regional lymph nodes is included, conventionally fractionated RT (25-28 fractions)

*acc. definition for boost irradiation

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

➢ Hypofractionation:

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

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


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

AGO\(^1\) 1b A +
DEGRO\(^1\) 1b A +/-

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

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

\(^1\)different interpretation of published data by AGO and DEGRO
### 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></th>
<th>Tamoxifen</th>
<th>Tamoxifen plus Radiotherapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>@10 yrs (95% C.I.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Guidelines Breast Version 2016.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boost-RT (improves local control, no survival benefit)</td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>1b B ++</td>
</tr>
<tr>
<td>40-60 years</td>
<td>1b B +</td>
</tr>
<tr>
<td>&gt; 60 years, if G3 or &gt;pT1</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Intraoperative irradiation (intraop APBI)</td>
<td></td>
</tr>
<tr>
<td>As boost-irradiation followed by WBI</td>
<td>2a B +</td>
</tr>
<tr>
<td>As sole radiotherapy modality (IORT 50 kV, IOERT)**</td>
<td></td>
</tr>
<tr>
<td>&gt;50 yrs**</td>
<td>1b B +/-*</td>
</tr>
<tr>
<td>&gt;70 yrs**</td>
<td>1b B +</td>
</tr>
<tr>
<td>Postoperative partial breast irradiation as sole radiotherapy modality (APBI)</td>
<td></td>
</tr>
<tr>
<td>Interstitial brachytherapy</td>
<td>1b B +/-*</td>
</tr>
<tr>
<td>&gt;70 yrs**</td>
<td>1b B +</td>
</tr>
<tr>
<td>Intracavity balloon technique</td>
<td>2b B -*</td>
</tr>
<tr>
<td>IMRT***</td>
<td>2b B -*</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>@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 Ipsilateral Breast Tumor Recurrence

| All patients | 12.0% (9.8–14.4) | 16.4% (14.1–18.8) | HR=0.65 (0.52–0.81); p<0.0001 |
| ≤40 years (Δ=11.6%) | 24.4% (14.9–33.8) | 36.0% (25.8–46.2) | HR=0.56 (0.34–0.92); p=0.003 |
| 41–50 years (Δ=5.9%) | 13.5% (9.5–17.5) | 19.4% (14.7–24.1%) | HR=0.66 (0.45–0.98); p=0.007 |
| 51–60 years (Δ=2.96%) | 10.3% (6.3–14.3) | 13.2% (9.8–16.7) | HR=0.69 (0.46–1.04); p=0.020 |
| >60 years (Δ=3.0%) | 9.7% (5.0–14.4) | 12.7% (7.4–18.0) | HR=0.66 (0.42–1.04); p=0.019 |

(Median F/U 17.2 y)

## EORTC 22881-10882: Boost vs no Boost
*(Endpoint: any first recurrence)*

<table>
<thead>
<tr>
<th></th>
<th>Boost (n=2,661)</th>
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</tr>
<tr>
<td>Cumulative Risk of Any First Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (Δ≥4%)</td>
<td>@15y 28.1% 32.8%</td>
<td>@20y 32.1% 38.7%</td>
<td>HR=0.92 (0.81-1.04), n.s.</td>
</tr>
<tr>
<td>≤40 years (Δ&gt;6%)</td>
<td>@15y 41.5% 49.5%</td>
<td>@20y 48.1% 56.8%</td>
<td>HR=0.80 (0.56-1.15), n.s.</td>
</tr>
<tr>
<td>41–50 years</td>
<td>@15y 34.0% 38.6%</td>
<td>@20y 35.6% 44.2%</td>
<td>HR=0.91 (0.71-1.16), n.s.</td>
</tr>
<tr>
<td>51–60 years</td>
<td>@15y 28.5% 34.7%</td>
<td>@20y 28.7% 36.2%</td>
<td>HR=0.96 (0.76-1.21), n.s.</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>@15y 27.4% 32.1%</td>
<td>@20y 29.1% 32.8%</td>
<td>HR=0.94 (0.74-1.19), n.s.</td>
</tr>
</tbody>
</table>

Postmastectomy Radiotherapy (PMRT)** to the Chest Wall

<table>
<thead>
<tr>
<th>Indication</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 tumor infiltrated lymph nodes (Lnn.)</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. high risk</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. low risk*</td>
<td>5 D +/-</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. (every risk) DEGRO¹</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>T3 / T4</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>pT3 pN0 R0 (and no additional risk factors)</td>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>If R0 is impossible to reach (for invasive tumor)</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>In young pts with high risk features</td>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td>Omission of RT if ypT0 ypN0 after NACT**</td>
<td>2b B +/-</td>
<td></td>
</tr>
</tbody>
</table>

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

¹different interpretation of published data by AGO and DEGRO

*For definition of risk, go to Further information; **Study participation recommended
## Radiotherapy of the Axilla

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor residuals after axillary dissection</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Sentinel node negative</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Axillary dissection not indicated e.g. cN0, SLN pos. (see chapter surgery)</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Extracapsular tumor spread (ECS)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Axillary micrometastases or isolated cells found in regional lymph nodes</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

---

Oxford / AGO LoE / GR
Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

<table>
<thead>
<tr>
<th>1-2 pos. SLN: Axillary dissection or RT of the axilla</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>if BCT and ACOSOG Z011-criteria fulfilled</td>
<td>1b B +/-*</td>
</tr>
<tr>
<td>No axillary treatment</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>if mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled</td>
<td>5 D +/-*</td>
</tr>
<tr>
<td>No further axillary treatment</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>if BCT and ACOSOG Z011-criteria not met</td>
<td>1b B ++*</td>
</tr>
<tr>
<td>if mastectomy: PMRT and ACOSOG Z0011-criteria not met, or PMRT not planned</td>
<td>1b B ++</td>
</tr>
</tbody>
</table>

>=3 pos. SLN:
- Axillary dissection 1b B ++
- Radiotherapy of the axilla 1b B +

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

RT to supra-/infraclavicular lymphatic regions

- ≥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)
  - AGO\(^1\) 2b B +/-

- After NACT/NAT if cN+ (indications acc. PMRT)
  - DEGRO\(^1\) 2b A +

\(^1\) 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
  - **2b B +/-**

- **After NACT/NAT if cN+ (ind. acc. PMRT)**
  - DEGRO
  - **2b A +**

---

1 different interpretation of published data by AGO and DEGRO
Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(_median follow-up 10.9 yrs)

<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
  - Oxford / AGO LoE / GR
  - 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 – (2/19)***

*Further information:*

**Search Strategy**
Search Terms: Radiotherapy Breast Cancer

**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.

**Preliminary Note (3/19)**

*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.


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


Adjuvant Radiotherapy - Slide 4/19

No further information

References:

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

Further information:

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

Update 2016:
According the St. Gallen-Consensus, 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)

References:


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

Further information:

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

Hypofractionation:

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

In 1 of 5 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\textsubscript{OS}=0.8; p=0.042)

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

Elderly patients should be counseled about:

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

References:


Radiotherapy in Elderly Patient Life Expectancy less than 10 Years (7/19)

Further information:

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs.;
We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival, and the biology of the tumor dictates the rate of IBTR, not the length of life.

References:

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


**BCS \( \geq 70y \) <4 cm cN0: Tamoxifen vs. Tamoxifen + RT (8/19)**

*Further information:*

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs. We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival; the biology of the tumor dictates the rate of IBTR, not the length of life.

*Reference:*

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

Further information:

The primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0.09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer. Young age and high-grade invasive ductal cancer were the most important risk factors for local relapse, in these patients the boost irradiation of 16 Gy significantly reduced the risk of relapse.

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

Reference:


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


Boost-RT in pts >60 years, if G3 or >T1 (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 1b B AGO+/-)


>70 yrs LoE 1b B 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 L\textsuperscript{1}, Meattini I\textsuperscript{2}, Marrazzo L\textsuperscript{3}, Simontacchi G\textsuperscript{1}, Pallotta S\textsuperscript{3}, Saieva C\textsuperscript{4}, Paier F\textsuperscript{1}, Scotti V\textsuperscript{1}, De Luca Cardillo C\textsuperscript{1}, Bastiani P\textsuperscript{2}, Orzalesi L\textsuperscript{6}, Casella D\textsuperscript{6}, Sanchez L\textsuperscript{6}, Nori J\textsuperscript{7}, Fambrini M\textsuperscript{8}, Bianchi S\textsuperscript{9}. 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.

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

Further information:

Primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0-09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer.

References:


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.”.


References according to the statements:

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

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


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


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 (13/19)**

*No further information*

**References:**

**References related to the statements:**

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

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

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


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 (14/19)

Further information:

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

References related to the statements:

1-2 pos SLN: BCT: No further treatment to the axilla neither axillary dissection nor RT of the axilla (criteria according ACOSOG Z011) (LoE 1b B, AGO+/−)


1-2 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) (15/19)

Further information:

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

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

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

References:


References related to the statements:

Supra-/infraclavicular lymphatic regions
RT to Supra-/infraclavicular lymphatic regions if ≥ 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 mammary ln. 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 16/19

No further information

References:

Internal mammaria lymph node region (IMN)

RT to Internal mammaria lymph node region (IMC) if pN0 high risk with central/medial tumors LoE 1b


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


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

No further information

References:

Concomitant Use of Systemic Therapy with Radiotherapy (18/19)

No further information

References:

Trastuzumab* concurrent with radiotherapy (LoE2b B AGO+) (*in HER2 pos tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT)


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


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


Other compounds (bevacizumab)

Interaction radiotherapy and smoking – Slide 19/19

No further information

References:

Guidelines Breast Cancer

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Therapy Side Effects
Therapy Side Effects

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

- **Version 2016:**
  Lück / Bischoff
Toxicity Assessment

Acute Toxicity
According to WHO¹ or NCI-CTC²

Grade

<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>
</tbody>
</table>

Recovery achieved

Long-Term Toxicity
No general assessment scale

¹ WHO Handbook for reporting results of cancer treatment, N0 48 (1979) (WHO offset Publications, Geneva)
# 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/ Stomatits</th>
<th>Cardiac Toxicity</th>
<th>Renal Toxicity</th>
<th>Hepatic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
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## Cytotoxic Anti-Cancer Drugs
### Acute Toxicity II

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Other side effects:
- **Myalgia**
- **Flue-like Synd., Edema**
- **Paravasate, Dexrazoxane**
- **Myalgia**
- **Myalgia**
- **Myalgia, Fluid retention, nails!**
- **Thrombophlebitis, Obstipation**
Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

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

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

Long-Term Toxicity
Cardiotoxicity

- Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)
  - B

- Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity
  - B

- Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently:
  - Elderly patients
  - Obesity
  - Hypertension
  - Hypercholesterolemia
  - Pre-existing cardiac diseases (incl. borderline LVEF)
  - Diabetes mellitus
  - B

- Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)
  - C  
  - +
Feasibility of Treatment Combinations Considering Toxicities

Regarding cardiac toxicity
- Trastuzumab simultaneous to radiotherapy 2b B +
- Trastuzumab simultaneous to epirubicin 2b B +/-
- Trastuzumab simultaneous to doxorubicin 2b B -
- Anthracycline simultaneous to radiotherapy 2c C -

Regarding lung and breast fibrosis
- Tamoxifen simultaneous to radiotherapy 3 C +/-
- Chemotherapy simultaneous to radiotherapy 1b B -
Side Effects of Trastuzumab/Pertuzumab Algorithm in Case of Cardiac Toxicity

- **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
      - CONTINUE treatment and repeat LVEF in 3 weeks
    - LVEF drop ≥10% points
      - HOLD treatment and repeat LVEF in 3 weeks

- **Not confirmed (LVEF drop ≤20% points or LVEF ≥50%)**
  - CONTINUE treatment

- **LVEF drop CONFIRMED (LVEF drop >20% points and LVEF ≥50%) or (LVEF drop <10% points and LVEF <50%)**
  - CONTINUE treatment and repeat LVEF in 3 weeks

- **LVEF drop CONFIRMED (LVEF drop ≥10% points and LVEF <50%)**
  - STOP treatment

- **Not confirmed (LVEF drop <10% points or LVEF ≥50%)**
  - RESUME treatment
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 2b
- Radiotherapy may moderately enhance the risk of ipsilateral lung cancer and angiosarcoma appearing 5–10 years after treatment 1a
  - Enhanced risk especially among ever smokers 2b
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  
  - Oxford / LoE: 2b
- Ovarian reserve of women who remain premenopausal after CTX is reduced  
  - Oxford / LoE: 2b
- CRA is associated with improved outcome (DFS/OS)  
  - Oxford / LoE: 1b

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
(Therapy Related) Fatigue

- Fatigue frequently present in breast cancer patients (30–60%)  
  2a B

- Exclusion of somatic reasons (anemia, tumor burden, co-morbidity, medication) for fatigue  
  1a A ++

- Psycho-social interventions specifically addressing fatigue are efficient in reducing fatigue  
  1a A ++

- Physical exercise with ambiguous effects regarding fatigue  
  1b D +

- Methylphenidate might improve fatigue  
  1a D +
(Therapy Associated)
Sleeping disturbance

- Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%)  
  2a B

- Behavioral therapies demonstrated efficacy in the treatment of insomnia and improved the quality of life  
  1b A ++
(Therapy Associated) Depression

- Depression is an often reported adverse event in breast cancer patients (20–30%)  
  Oxford /LoE: 2a B

- Psychological interventions are effective to improve mood, but not survival in distressed and depressed patients  
  Oxford /LoE: 1b A

- Antidepressents have shown to improve depression in breast cancer patients  
  Oxford /LoE: 1b A

- Regular exercise participation can prevent depression among breast cancer survivors  
  Oxford /LoE: 2b B +
(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
  - 2b B

- Methylphenidate might improve cognitive function in patients with cancer
  - 3a C
## Side-effects and Toxicity of Endocrine Agents

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Guidelines Breast
Version 2016.1

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)

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Key-Toxicities – Antibodies/Antibody-drug-conjugates

**Trastuzumab**
- Cardiotoxicity in the adjuvant setting (0.8–4.0%)
- Troponin I might identify patients who are at risk for cardiotoxicity

**Bevacizumab**
- Hypertonus, proteinuria, bleeding, left ventricular dysfunction,
Small Molecules

Lapatinib
- Diarrhea, skin rash, fatigue

Everolimus
- Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, thrombocytopenia

PARP-inhibitors (olaparib)
- Fatigue, myelosuppression

CDK4/6 inhibitors (palbociclip, LEE011)
- Myelosuppression, neutropenia
Immun-Checkpoint Inhibitors

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

- **Side effects ≥ Grad 3**
  - Diarrhoe
  - Fatigue
  - Colitis
  - Hypophysitis
  - Hepatitis
  - Skin changes
  - Thyreoiditis
Further information:


Screened guidelines:

No references
Toxicity Assessment (3/24)

Further information:

Acute toxicity and in most cases 100 day mortality rates are well documented in the majority of phase III trials. Toxicities are graded according to WHO or NCI standards. This implies that toxicities concerning liver, kidney heart or skin are well documented and graded. Other toxicities like fatigue, depression, menopausal symptoms or impairment of cognitive function are systematically underreported by these tools. Most trials end five or ten years after the last patient in, such that late and very late effects are rarely documented.

Acute Toxicity according to WHO1 or NCI-CTC2:

References:

2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010); http://evs.nci.nih.gov/ftp1/CTCAE/About.html
Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (4/24)

No further information

References:

No further information

References:
see slide 4
No further information

No references
**Long-Term Toxicity Cardiotoxicity I (7/24)**

**Further information:**

Anthraclycline (A) based standard chemotherapy regimens as used in the adjuvant therapy of breast cancer are associated with a relatively low acute toxicity and treatment related mortality rates < 1%. In terms of long-term toxicity cardiotoxicity and secondary acute leukemia/MDS are clinically relevant.

**Cardiotoxicity:**

Early cardiotoxicity of anthracyclines has been well established in clinical trials. Limited data are available on long-term cardiac safety of A based regimens. As patients with breast cancer are getting older and as survival rates improve long term cardiotoxicity is of growing interest.

**AC:** Among patients treated with four cycles of AC on NSABP B31 17% of patients developed asymptomatic cardiac disease defined as the decline in left ventricular ejection fraction of more than 10% to an ejection fraction of less than 55%. Similar data were presented recently by Perez et al. in N9831 trial. In 2992 patients completed AC 5% had LVEF decrease disallowing trastuzumab (decrease below normal: 2.4%, decrease > 15%: 2.6%).

**FAC:** The Southwest Oncology Group evaluated long term cardiotoxicity from patients randomized to protocol S8897. In this trial patients were randomized to CAF or to CMF. A was given on day 1 and 8. 180 patients from an potential sample of 1176 patients entered. There was no significant difference in the proportion of women with an LVEF less than 50% at 5 to 8 years (CAF vs. CMF: 8% vs. 5%, p=0.68) or at 10 to 13 years (CAF vs. CMF: 3% vs. 0%, p=0.16). However in an exploratory analysis the mean LVEF in the doxorubicin group was statistically significantly lower in the 5 to 8 year sample (p=0.01), but not in the 10 to 13 year sample.

**French FEC:** The FASG reports ten year follow–up data in patients receiving either FE50C or FE100C from FASG 05. Delayed (> 1 month after the end of chemotherapy) symptomatic cardiotoxicity was reported in 1.5% of patients from the FE50C arm and in 1.1% of patients from the FE100C arm. In summary early and delayed cardiotoxicity was reported in 4.3% and in 4.8% of patients.
The second analysis from the FASG trials compared E+ and E- (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:**


“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:


Feasibility of Treatment Combinations Considering Toxicities (8/24)

Further information:

The frequency of adverse events for patients with HER-2 positive early breast cancer was examined in a randomized study with a median follow-up time of 3.7 years. 1503 patients were irradiated. Radiotherapy (RT) was administered either without or with concurrent trastuzumab (H). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of cardiac events (CEs) regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% v 5.9% with or without RT, respectively. Thus, concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (Halyard al, 2009). Reported data regarding the influence of tamoxifen given simultaneously to radiotherapy are diverging. Simultaneously given tamoxifen to radiotherapy might increase the risk of Grade 1 lung fibrosis (p = 0.01) and might increase the risk of late lung sequelae (OR = 2.442, 95% CI 1.120-5.326, p = 0.025). However other reports did not confirm such an connection. Therefore the results of the ongoing CONSeT-trials has to be awaited.

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 and Pertuzumab: Algorithm in Case of Cardiac Toxicity (9/24)**

*Further information:*

Cardiotoxicity has been reported to occur with trastuzumab when administered alone and in combination with antineoplastic agents, particularly anthracyclines. The risk of cardiotoxicity with trastuzumab has been reported to be 4% with monotherapy and 27% when administered in combination with an anthracycline and cyclophosphamide. However, severe and life-threatening damages are rare and the majority of reported cardiac effects are mild to moderate, nonspecific, and medically manageable. Signs and symptoms are similar to those observed in patients who develop anthracycline-induced cardiomyopathy and include tachycardia, palpitations, and exertional dyspnea, which may ultimately progress to congestive heart failure (Keefe, 2002). Trastuzumab-associated toxicity usually responds to standard treatment or the discontinuation of trastuzumab, and there is no evidence that the toxicity is dose related. Left ventricular ejection fraction (LVEF) should be measured at baseline and at regular intervals. An algorithm based on LVEF changes is presented to aid in the question whether continuation of trastuzumab is safe and feasible or whether discontinuation is warranted.

There are also data for trastuzumab and pertuzumab from phase 2 trials and randomized phase 3 trials, in neither trial cardiotoxicity was increased through the addition of pertuzumab to trastuzumab both in the absence or presence of taxane containing chemotherapy. In the Cleopatra trial 808 pts with metastatic breast cancer were randomized to docetaxel and trastuzumab and placebo or to docetaxel and trastuzumab and pertuzumab. LVEF dysfunction (any grade) was more frequently seen in the placebo group than in the pertuzumab group (8,3% vs 4,4%). LVEF dysfunction of grade 3 or higher was reported in 2,8% and 1,2% of the patients in the placebo and pertuzumab arms respectively.

*References:*

Secondary Malignancies I (10/24)

Further information:

Approximately one in every 20 breast cancer patients developed a second non-breast primary tumor 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. Mitoxantrone-based chemotherapy was associated with a higher leukemic risk than with anthracyclines (RR 16.8, 95% CI 7.1 to 34.2 than RR 2.7, 95% CI 1.7 to 4.5). Epirubicin and doxorubicin had a similar risk. 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.
US – AC

Purpose: We reviewed data from all adjuvant NSABP breast cancer trials that tested regimens containing both doxorubicin (A) and cyclophosphamide (C) to characterize the incidence of subsequent acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Materials and Methods: Six complete NSABP trials have investigated AC regimens (B-15, B-16, B-18, B-22, B-23, and B-25). Six distinct AC regimens have been tested and are distinguished by differences in cyclophosphamide intensity, cumulative dose and by the presence or absence of mandated prophylactic support with growth factor and ciprofloxacin. In all regimens, A was given at 60 mg/m² q 21 days x 4. C was given as follows: 600 mg/m² q 21 days x 4 ("standard AC"); 1200 mg² q 21 days x 2; 1200 mg/m² q 21 days x 4; 2400 mg/m² q 21 days x 2; and 2400 mg/m² q 21 days x 4. Occurrence of AML/MDS was summarized by incidence per 1,000 patient-years at risk and by cumulative incidence. Rates were compared across regimens, by age, and by treatment with or without breast radiotherapy.

Results: The incidence of AML/MDS was sharply elevated in the more intense regimens. In patients receiving two or four cycles of C at 2400 mg/m² with granulocyte colony-stimulating factor (G-CSF) support, cumulative incidence of AML/MDS at 5 years was 1.01 % (95 % confidence interval [CI], 0.63 % to 1.62 %), compared with 0.21 % (95 % CI, 0.11 % to 0.41 %) for patients treated with standard AC. Patients who received breast radiotherapy experienced more secondary AML/MDS than those who did not (RR = 2.38, P = .006), and the data indicated that G-CSF may also be independently correlated with increased risk.

AML/MDS in older patients
In summary Conclusion for FEC and :AC secondary AML/MDS rates correlate with regimens employing intensified doses of cyclophosphamide requiring, G-CSF support and to a smaller extent which were characterized by increased rates of subsequent AML/MDS, although the incidence of AML/MDS was small relative to that of breast cancer relapse. Breast radiotherapy appeared to be associated with an increased risk of AML/MDS, but data are inconsistent (see slide 10/20).

References for statements 1-4:


Reference for Statement Tamoxifen and endometrial cancer

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). According to the cohort data of the SEER registries 1973 to 2000 risk for second cancers was dose dependend. Radiotherapy treatment assuming standard protocol with 50Gy tumour dose and beem energy 6 MV photons. The RR were 1.45 (95%CI 1.33 to 1.58) for high dose second cancer sites (1 +Gy, lung, oesophagus, pleuro, bone and soft tissue sarcoma) with no evidence of elevated risk for sites receiving medium (05.-0,9 Gy) or low doses (< 0,5 Gy). Overall risks were generally lower for patients treated in recent years (1993 +). But the pattern of risks observed were consistend with the general literature on radiation carcinogenesis, risks were higher for sites that should have received higher doses and also higher for young age at exposure. 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. Data are inconsistent for an elevated risk of AML/MDS after radiation exposure.

References:


Chemotherapy Related Amenorrhea (CRA) (12/24)

_Further information:_

**Synonyma:** Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)

Preservation of ovarian function is an important issue in the population of breast cancer patients especially in the patient younger than 40. Up to now neither data for ovarian protection with e.g. GnRH analogues nor cryopreservation of ovarian tissue are convincing. The treatment compromising most oftenly fertility is chemotherapy.\(^1\) After modern taxan-anthracyclin containing chemotherapy the risk of CRA is markedly lower compared to older chemotherapy regimens. Especially in younger patients the restitution of menses after 2 years is greater than 90 %.\(^2\)

However one third of the patients probably will be infertile after chemotherapy. The effects are more pronounced the older the patient and the longer the chemotherapy.

Data from the NSABBP B-30 trial (sequential versus concurrent ACT, doxorubicin-docetaxel in women with operable, node-positive, early stage breast cancer) amenorrhoe in premenopausal women was associated with improved disease-free and overall survival regardless of treatment, in particular when the tumor was ER-positive.\(^3,4\) The dose of drug delivered was not a key factor explaining the differences.\(^4\)

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.....**


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


Further information

Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al, 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al, 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al, 2005). Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al, 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al, 2010).

The biologic base for these changes is unclear. However, are there several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms (Ahles et al, 2007). Cognitive behavioral therapy might lead to significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 2-month and 6-month follow-ups (Ferguson et al, 2007). Other potential treatment approaches include methylphenidate, which has been used to improve cognitive
function in patients with advanced cancer. E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R130#R130

E:\Dokumente und Einstellungen\ute\Lokale Einstellungen\Temp\Literatur Nebenwirkungen\Bower, behavioral symptoms in breast cancer survivors 2008.htm - R110#R110

References:

Therapy-related cognitive deficits (chemobrain)...


**Cognitive-behavioral therapy**


**Methylphenidate might improve cognitive function**

Side-effects and Toxicity of Endocrine Agents I (17/24)

Further information:

In a metaanalysis on 19.818 pts. treated with 3rd generation aromatase inhibitors the risk of developing cardiovascular adverse events was slightly higher in comparison to tamoxifen with an RR of 1.34 translating into a minimal risk of 0.5%.
(Cuppone F et al 2008)
In an actual systematic review and metaanalysis of 30.023 patients in 7 trials comparing aromatase inhibitors with tamoxifen, the increased risk for developing cardiovascular disease (OR=1.26) for aromatase inhibitors was confirmed, as well as the occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

References:

Side-Effects and Toxicity – of Bone Modifying Agents (BMA, Bisphosphonates, Denosumab) (18/24)

Further information:

A recently published randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases. In terms of toxicity rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; P = .39) (Stopeck et al, 2010). In a pooled analysis of three randomized phase III trials of denosumab versus zoledronic acid in patients treated for metastatic cancer this occurrence rate for denosumab was confirmed with 1.67% (RR= 1.61) (Van den Wyngaert et al, 2011).

Although there amounting data, that bisphosphonates might have anticancer benefits for older postmenopausal women, the routine use of bisphosphonates as adjuvant treatment for patients with early breast cancer is not recommended (Paterson et al 2012; Wong et al 2012).

References:


Acute phase rea
Gastrointestinal side effects...

Recommendations for Precautions to Prevent ONJ (19/24)

Further information:

The reported incidence of osteonecrosis of the jaw (ONJ) ranges from 0.94% to 18.6%. A study with 1,621 patients who received 29,006 intravenous doses of BP, given monthly reported an crude ONJ incidence of 8.5%, 3.1%, and 4.9% in patients with multiple myeloma, breast cancer, and prostate cancer, respectively. Patients with breast cancer demonstrated a reduced risk for ONJ development, which turned out to be non-significant after adjustment for other variables. Multivariate analysis demonstrated that use of dentures (aOR = 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR = 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR = 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR = 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development.

Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP. In conclusion, validated dental extractions and use of dentures are risk factors for ONJ development. Ibandronate and pamidronate at the dosages and frequency used in this study seem to exhibit a safer drug profile concerning ONJ complication; however, randomized controlled trials are needed to validate these results. Before initiation of a bisphosphonate, patients should have a comprehensive dental examination.

References:


Frequent Side Effects of Bone Modifying Agents (BMA) (20/24)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

Go to slide 18-19/22!
Key-Toxicities Antibodies/Antibody-drug-conjugates – Small Molecules (21/24) and (22/24)

Further information:

In the HERA trial, the incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% v 0.0%; confirmed significant LVEF decreases, 3.6% v 0.6%). In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery; of these 59 patients, 52 were considered by the cardiac advisory board (CAB) to have a favorable outcome from the cardiac end point. The incidence of cardiac end points remains low even after longer-term follow-up and the majority of cardiac events resolved (Procter et al, 2010).

In the NSABP B-31- and NCCTG 9831-trial trastuzumab-treated patients had a 2.0% incidence of symptomatic heart failure events compared with 0.45% in the chemotherapy-alone arm. Complete or partial recovery was observed in 86.1% of trastuzumab-treated patients with symptomatic heart failure events after cessation of trastuzumab. Independent predictors for cardiac events were age older than 50 years, a low ejection fraction at the start of paclitaxel treatment, and trastuzumab treatment. The majority of these patients recover with appropriate treatment (Russell et al, 2010).

The usefulness of troponin I in the identification of patients at risk for trastuzumab induced cardiotoxicity (TIC) and in the prediction of LVEF recovery was investigated in 251 women treated with trastuzumab. TNI was measured before and after each trastuzumab cycle. TIC occurred more frequent in patients with troponin elevation (TNI+; 62% v 5%; P < .001). Thus, Troponin increase identifies trastuzumab-treated patients who are at risk for cardiotoxicity and are unlikely to recover from cardiac dysfunction despite HF therapy.

In the Phase III trial of Capecitabine with or without the oral 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 bavcizumab alone or in combination with chemotherapy in metastatic breast cancer showed a statistically significant bevacizumab associated increased risk for proteinuria (OR=27.68), hypertension (OR=12.76), left ventricular dysfunction (OR=2.25) and hemorrhagic events (OR=4.07), while no increased incidence was found for gastrointestinal perforation, vascular or fatal events and febrile neutropenia, respectively.

References

Cardiotoxicity....


Troponin I...


Bevacizumab ....


Lapatinib...


**Pertuzumab**


**T-DM1**


**Everolimus:**

Immun-Checkpoint Inhibitors (23-24/24)

No further information

No references
Supportive Care
Supportive Care

- **Version 2002:**
  Diel

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

- **Version 2016:**
  Diel / Möbus
Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients.

We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language.

Special emphasis is put on aspects concerning breast cancer patients

In the German environment, special interest is earnt by the publications of the „Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG: http://www.onkosupport.de“

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

## Erythropoiesis-stimulating agents (ESAs)

<table>
<thead>
<tr>
<th>Oxford / LoE / AGO</th>
<th>Guidelines Breast Version 2016.1</th>
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<tbody>
<tr>
<td><strong>Indicated in asymptomatic anaemia</strong></td>
<td>1a B -</td>
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<td>- In dose-dense / dose-escalated CT (iddETC)</td>
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<tr>
<td><strong>Indicated in symptomatic anaemia</strong></td>
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<td>- In the adjuvant setting</td>
<td>1b A +</td>
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<td>- In the neoadjuvant/metastatic setting</td>
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<tr>
<td><strong>Treatment and secondary prophylaxis of chemotherapy induced anemia (CIA)</strong></td>
<td>1a A +</td>
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<td><strong>Improvement of outcome (DFS, OS)</strong></td>
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<td><strong>Treatment start at Hb-levels approaching &lt; 10 g/dL</strong></td>
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<td><strong>Target Hb 11–12 g/dL</strong></td>
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<td><strong>Thromboembolic events are increased with ESAs</strong></td>
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Practical Use of ESAs

- Epoetin α and Darbepoetin are equieffective

**Dose:**
- Epoetin α: 150 IU/kg 3 x weekly s.c. or
  40.000 IU 1 x /week s.c.
- Epoetin α: 80.000 IU q2w s.c. or
  120.000 IU q3w s.c.
- Darbepoetin: 2,25 µg/kg s.c. weekly
- Darbepoetin: 500 µg s.c. q3w

- Hb measurements weekly
  - Dose reduction at Hb-increase > 1g/dl within 2 weeks
  - Dose increase at Hb-increase < 1g/dl within 4-6 weeks

- In case of FID give IV iron supplementation
- p.o. iron supplementation
- STOP ESA-treatment in case of missing increases of Hb-levels after 9 weeks

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Relevant Guidelines


Prophylaxis of Infections

NB Rarely Applicable to Patients with Solid Tumors (e.g. BC)
ASCO Practice Guideline „Antimicrobial Prophylaxis...“ 2013

- Avoidance of highly infection-risking behaviour or situations 5 D +
- Prophylactic treatment in low risk patients 1a B -
- Prophylactic treatment in high risk* patients (e.g. according to NCCN Guidelines) with
  - Antibiotics 1a A ++
  - Anti-fungal agents (triazole) 1a B +/-
  - Virostatics in solid tumors 5 D -
  - Granulocyte colony-stimulating factors 1a A ++

* High risk definition: estimated duration of neutropenia < 100/µl > 7d
Step 1: Assess frequency of FN associated with the planned chemotherapy regimen

- FN risk ≥20%
- FN risk 10-20%
- FN risk <10%

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

High risk:
- Age >65 years

Increased risk:
- 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

Mucositis

Desinfecting / antiphlogistic measures:
Mouth rinsing with infusions of camomile or salvia, extracts of camomile, etheric oils, polyvidon-iodine, hexetidine. Local therapy with crystal violet solution 0.5% or tinctura myrrhei, H. mometasonfuroate + propylene glycol

Mucosa protecting measures (during / after application of chemotherapy):
Sucking ice cubes (especially from pineapple juice) during 5-fluorouracile- or HD-melphalane. Calcium folinate (Leucovorin-Mundgel®) every 4–6 hrs for HD-methotrexate: do not start earlier than 24 hours after end of MTX-Infusion (otherwise potential loss of efficacy of MTX!). Dexpanthenole (Panthenol®-Solution. 5%) mouth rinsing.

Local antimycotic treatment:
Amphotericine B, nystatine, fluconazole

Local antiviral treatment
Aminoquinuride / tetracaine-HCl , Aciclovir®

Local anaesthesia:
Benzocaine PO

Granulocyte Colony-stimulating Factors

- 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
Relevant Guidelines

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/mm\(^3\) or expected to fall to <500 cells/mm)

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Daily evaluation</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Hospitalization of high risk patients</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Homecare in low risk patients</td>
<td>1b A +</td>
</tr>
<tr>
<td>Differential blood count</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Imaging of lungs</td>
<td>3 C ++</td>
</tr>
<tr>
<td>Immediate initial empiric antibiotic therapy</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Empiric antifungal therapy 4–7d in case of failure of antibiotic therapy</td>
<td>1b A ++</td>
</tr>
<tr>
<td>G-CSF for treatment (not prophylactic)</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>
Calculated Antibiotic Therapy in FN

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

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

- Treatment of anthracycline extravasation
- In cardiac risk patients
  - Consider alternative regimens (anthracycline-free, liposomal)

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

Oxford / AGO
LoE / GR

- 2b B ++
- 5 D ++
Paravasation
Dexrazoxane

Day 1: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 2: 1000 mg/m² (max. 2000 mg), IV 1–2 hrs
Day 3: 500 mg/m² (max. 1000 mg), IV 1–2 hrs

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

1. Local cooling: ice packs for 15 min every 6 hrs, for at least 3 days, alternatively: 24 h continuous ice cooling

2. Local application (with swab) of dimethylsulfoxid 99% (DMSO) every 3-4 hours for at least 3 days (better 14 days), allow it to dry on air. The interval may be extended to 6 hours from day 4 onward.
### Antiemetic Therapy

MASCC/ESMO antiemetic-guidelines  
NCCN guidelines

<table>
<thead>
<tr>
<th></th>
<th>Oxford / AGO</th>
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<tbody>
<tr>
<td>LoE / GR</td>
<td></td>
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<tr>
<td>After assessment of emetic potential of chemotherapy protocol</td>
<td>5</td>
</tr>
<tr>
<td>Neurokinin-1-receptor-antagonists</td>
<td>1b</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1a</td>
</tr>
<tr>
<td>5-HT$_3$-antagonists</td>
<td>1b</td>
</tr>
<tr>
<td>Fixed antiemetic combination therapy</td>
<td>1b</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>3b</td>
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</tbody>
</table>

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in der DGGG e.V.  
sowie  
in der DKG e.V.  
Guidelines Breast  
Version 2016.1
Supportive Therapy

Antiemetics


### Supportive Therapy
#### Antiemetics

<table>
<thead>
<tr>
<th>Wirkstoffgruppe</th>
<th>Substanz</th>
<th>Dosierung</th>
<th>Nebenwirkungen</th>
<th>Potenzial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotoninantagonisten</td>
<td>Ondansetron</td>
<td>8 mg i.v., 2 x 4-8 mg p.o., transdermal</td>
<td>Kopfschmerzen, Diarrhoe, Flusssymptomatik, Transaminasenanstieg, Darmatonie in hoher Dosierung</td>
<td>sehr hoch</td>
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<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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<td></td>
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<tr>
<td></td>
<td>Palonosetron</td>
<td>0, 25 mg i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Serotoninantagonisten</strong>: Ondansetron, Tropisetron, Granisetron, Palonosetron</td>
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<td><strong>NK 1-Antagonisten</strong>: Aprepitant, Fosaprepitant</td>
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<td></td>
<td><strong>Dopaminantagonisten/substituierte Benzamide</strong>: Metoclopramid, Alizaprid</td>
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<td><strong>Phenothiazine/Butyrophenone</strong>: Haloperidol, Dexamethason, Prednisolon</td>
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<td></td>
<td><strong>Corticosteroide</strong>: Dexamethason, Prednisolon</td>
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<td></td>
<td></td>
<td></td>
<td><strong>NEPA (Netupitant and Palonosetron)</strong>: NE 300 mg PA 0,5 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Nebenwirkungen:** Kopfschmerzen, Flusssymptomatik, Transaminasenanstieg, Darmatonie in hoher Dosierung, Cytochrom-P-450-Aktivierung mit Dosisreduktion von Dexamethason (2 x 8 mg), Keine Kombination mit Astemizol, Terfenadin, Cisaprid, Dyskinesien (Antidot: Biperiden), Angstreaktion, Depressionen, Diarrhoe, Sedation, Senkung der Kompfrschwelle, transiente Leberwerterhöhung, Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg.

**Potenzial:** sehr hoch, hoch,mäßig,sehr hoch.
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 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

- **Swelling agents**
  - Psyllium, flaxseed (shredded)

- **Osmotic laxatives**
  - Macrogol > Lactulose (Cochrane review LoE 1a, AGO +)
  - Oral radio-opaque material: ultima ratio e.g. sodium amidotrizoate
  - Sorbite

- **Motility stimulating laxatives**
  - Sennae, Ricinus, Bisacodyl, sodium-picosulfate

- **Emollients** (Internal lubricants e.g. paraffin)

- **Opioid-receptor-antagonists (in opioid-related constipation)**
  - MethylNaltrexone
Palliative Care

- “…expert consensus that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.”¹

- “Palliative care should be initiated by the primary oncology team and augmented by collaboration with an interdisciplinary team of palliative care experts.”²

- “Expert palliative care, including effective control of pain and other symptoms, should be a priority.”³

¹ Smith et al, J Clin Oncol 30 880-887, 2012
Supportive Care (2/23)

No further information

No references
Guideline spectrum (3/23)

Further information:

Specific national and international guidelines deal with various aspects of evidence-based supportive therapy of cancer patients.
We try to quote these guidelines wherever appropriate, but underline that the listings of relevant guidelines do not claim to be complete. The listing is clearly biased towards German and English language.
Special emphasis is put on aspects concerning breast cancer patients.
In the German environment, special interest is earned by the publications of Arbeitsgem. Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin der DKG: http://www.onkosupport.de

No references
**Erythropoiesis-Stimulating Agents (ESAs) (4/23)**

*Further information:*

Prior to 2007, the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa were indicated for use in chemotherapy-induced anemia to achieve target hemoglobin (Hb) levels of approximately 12 grams per deciliter (gm per dL), and treatment was to be withheld if Hb exceeded 13 gm per dL. In March 2007, the FDA changed the labeling of the ESAs to add boxed warnings, updated in November 2007, to include the following key points: (a) ESAs should be used only to treat anemia that occurs in patients with cancer while they are undergoing chemotherapy; (b) treatment with ESAs should be stopped when chemotherapy ends; and (c) dosing ESAs to an Hb target of 12 gm per dL or greater has resulted in more rapid cancer progression or shortened overall survival in patients with breast, head and neck, lymphoid, cervical, and non-small cell lung malignancies. In January 2008, the FDA specified that the increased risk of more rapid tumor growth or shortened survival was associated with ESAs when "administered in an attempt to achieve a Hb level of 12 gm per dL or greater, although many patients did not reach that level." A new black-box warning regarding this association was added to the labels of the ESAs in March 2008, and the FDA mandated further label changes on July 30, 2008, that ESA therapy should not be initiated in patients receiving chemotherapy at Hb levels of 10 gm per dL or higher.

**OBJECTIVE:** To (a) assess the prevalence and predictors of ESA administrations at Hb levels above 12 gm per dL among patients with a diagnosis of solid or hematologic cancer or myelodysplastic syndrome who began their first regimen of conventional myelosuppressive chemotherapy between 2002 and 2006, and (b) describe patterns of ESA treatment subsequent to the first ESA administration at Hb above 12 gm per dL.

In 2012 a Cochrane review was published by Tonia et al., extracting data from a total of 91 trials with 20,102 participants to perform a systematic review, concluding that ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths. There is suggestive evidence that ESAs may improve QoL. Whether and how ESAs affects tumour control remains uncertain. The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient’s clinical circumstances and preferences. More data are needed for the effect of these drugs on quality of life and tumour progression. Further research is needed to clarify cellular and molecular mechanisms and pathways of the effects of ESAs on thrombogenesis and their potential effects on tumour growth.
References:


Further references:

Statement: An increased mortality and tumor progression by the use of ESF can not be safely ruled out

levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study, J Clin Oncol. 2005 Sep 1;23(25):5960-72

Relevant Guidelines:

Practical Use of ESAs (5/23)

Further information:

For practical use refer to relevant practice guidelines
The increased risk of death and thromboembolic events should be balanced against the potential benefits of ESA treatment taking into account each patient’s clinical circumstances and preferences.

References:

Relevant guidelines (6/23)

No further information

References:

Prophylaxis of Infection (7/23)

Further information:

According to relevant guidelines, antibiotic prophylaxis of asymptomatic patients under chemotherapy should be restricted to high risk cases: one selective criterion could be expected duration of neutropenia of greater than 10 days (NCCN). (ASCO absolute neutrophil count < 100/µl > 7 days) N.B.: Standard chemotherapy protocols such as used in breast cancer patients do not regularly justify antibiotic prophylaxis.

The use of oral prophylactic antibiotics in patients with neutropenia is controversial and not recommended by the Australian Consensus Guidelines 2011 Steering Committee because of a lack of evidence showing a reduction in mortality and concerns that such practice promotes antimicrobial resistance. Recent evidence has demonstrated non-significant but consistent, improvement in all-cause mortality when fluoroquinolones (FQs) are used as primary prophylaxis. However, the consensus was that this evidence was not strong enough to recommend prophylaxis.

Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol 1998;16:1179-1187: In a meta-analysis that evaluated 18 trials (N=1408) in which fluoroquinolones were compared to either placebo or TMP/SMX, fluoroquinolone prophylaxis significantly reduced the incidence of Gram-negative infections by about 80% compared with those without prophylaxis (relative risk=0.21; 95% CI, 0.12-0.37), leading to an overall reduction in total infections.

Latest update: in the latest ASCO Guideline on Antimicrobial Prophylaxis and Outpatient Management… (2013) the use of antimicrobial prophylaxis is only recommended for patients expected to have 100 neutrophils/µL for 7 days, unless other factors increase risks for complications or mortality to similar levels. The authors clearly state, that chemotherapy for solid tumors rarely leads to the mentioned conditions. An oral fluoroquinolone is preferred for antibacterial prophylaxis and an oral triazole for antifungal prophylaxis. The guideline encourages the use of myeloid growth factor prophylaxis to render antimicrobial prophylaxis unnecessary.

Interventions such as footwear exchange, protected environments, respiratory or surgical masks, neutropenic diet, or nutritional supplements are not recommended because evidence is lacking of clinical benefits to patients from their use.
References:


Relevant Guidelines

Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline. Christopher R. Flowers, Jerome Seidenfeld, Eric J. Bow, Clare Karten, Charise Gleason, Douglas K. Hawley, Nicole M. Kuderer, Amelia A. Langston, Kieren A. Marr, Kenneth V.I. Rolston, and Scott D. Ramsey
No further information

No references
Relevant guidelines (9/23)

No further information

Reference:

**Mucositis (10/23)**

**Further information:**


Die Pathogenese der Mukositis ist nicht vollständig geklärt. Diagnostik, Therapie und Prophylaxe werden bisher nicht standardisiert durchgeführt und sind hauptsächlich auf die Symptomkontrolle ausgerichtet.“

**References:**

*Relevant Guidelines*

**Granulocyte Colony-stimulating Factors (11/23)**

*Further information:*

The ability to deliver the planned dose and intensity of chemotherapy (the amount of drug administered/unit of time) is important for tumor control and survival. In clinical practice, neutropenic events are the main limiting factors towards achieving this aim. Furthermore, severe neutropenia accompanied by fever, so called „febrile neutropenia (FN)“, is the most serious manifestation of neutropenia usually requiring hospitalization and intravenous antibiotics. Without stringent management FN is associated with significant morbidity and mortality. The primary use of recombinant granulocyte colony-stimulating factors has reduced the incidence of febrile neutropenia during dose-dense adjuvant/neoadjuvant chemotherapy programs for breast cancer.

In 2012, a Cochrane review sought to assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer. The authors concluded that „In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefit in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects.“

In a comparative effectiveness study, pegfilgrastim prophylaxis was associated with a reduced risk of neutropenia-related or all-cause hospitalization relative to filgrastim prophylaxis. A recent study demonstrated in high risk breast cancer that 6 mg lipegfilgrastim, a novel glyco-pegylated granulocyte-colony stimulating factor, was as effective as pegfilgrastim in reducing neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy.
References:


Relevant Guidelines:

ASCO:
Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff


NCCN:


Stimulation der Granulopoese mit G-CSF

Relevant guidelines (12/23)

No further information

References:

Management of Febrile Neutropenia (13/23)

Further information:

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

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

References:


Relevant Guidelines:

ASCO:
Thomas J. Smith (Chair), James Khatcheressian, Gary H. Lyman, Howard Ozer, James O. Armitage, Lodovico Balducci, Charles L. Bennett, Scott B. Cantor, Jeffrey Crawford, Scott J. Cross, George Demetri, Christopher E. Desch, Philip A. Pizzo, Charles A. Schiffer, Lee Schwartzberg, Mark R. Somerfield, George Somlo, James C. Wade, James L. Wade, Rodger J. Winn, Antoinette J. Wozniak, and Antonio C. Wolff

NCCN:


Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)
**Calculated Antibiotic Therapy in FN (14/23)**

*Further information:*

The most important treatment aspect is to initiate calculated antibiotic treatment as soon as possible, but no later than 2 hours after onset of fever, according to updated guidelines. Recommendations need to be regularly updated according to the changes in microbial sensitivity and resistance towards antiinfective treatments.

*References:*

*Relevant practice guidelines:*

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)
**Dexrazoxane (15/23)**

*Further information:*

Anthracyclines are among the most active chemotherapeutic agents in cancer treatment. Although infrequent, cumulative dose-dependent cardiotoxicity is nevertheless a significant side effect of this therapy resulting in reduced cardiac reserve or even frank cardiac failure. Although used in several types of malignancy, anthracyclines are most commonly used in breast cancer treatment. Importantly, recent advances have also seen the increasing use of another cardiotoxic agent, the monoclonal antibody trastuzumab, both in the metastatic as well as in the adjuvant breast cancer setting. A great number of studies review and discusses the relationship of cardiotoxicity and anthracycline use, particularly in the breast cancer setting, and explores available treatment options for the anthracycline-treated patients based on evidence from recent Phase III trials. Dexrazoxane is not recommended for routine use in breast cancer (BC) in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Consider use with metastatic BC and other malignancies, for patients who have received more than 300 mg/m(2) doxorubicin who may benefit from continued doxorubicin-containing therapy. Cardiac monitoring should continue in patients receiving doxorubicin.

A Cochrane review investigated Cardioprotective interventions for cancer patients receiving anthracyclines and concluded: “The nine included studies of dexrazoxane enrolled 1403 patients. The meta-analysis of dexrazoxane showed a statistically significant benefit in favour of dexrazoxane for the occurrence of heart failure (Relative Risk (RR) 0.29, 95% CI 0.20 to 0.41). No evidence was found for a difference in response rate or survival between the dexrazoxane and control group. Only for one adverse effect (abnormal white blood cell count at nadir) a difference in favour of the control group was identified.”

*References:*


**Paravasation Dexrazoxane (16/23)**

*Further information:*

Although indicated and approved for cardioprotection, dexrazoxane has been suggested as being helpful in the case of anthracyclin paravasation. The agent is administered systemically.

*References:*

*Relevant practice guideline*

Zytostatika-induzierte Paravasate - Empfehlungen zu Diagnose, Prophylaxe und Therapie [ PDF-Datei ]
Arbeitsversion der ASORS Paravasate-Guidelines (Stand April 2010)
Maike de Wit, Petra Ortner, Hans-Peter Lipp, Jalid Sehouli, Michael Untch, Markus Ruhnke, Regine Mayer-Steinacker, Carsten Bokemeyer, Karin Jordan
download: http://www.onkosupport.de/e974/e2538/e3782/e3494/ASORS_AV_Paravasate-Guidelines_04-2010.pdf

Witte J, de Wit M.
Prävention, Diagnostik und Therapie der zytostatikaassozierten Paravasation - Was tun wenn’s brennt?
Im Focus Onkologie 2010;6:50-55.
Further information:

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

The combination of ondansetron, dexamethasone and aprepitant is able to protect 66–78% of patients from emesis and 48–49% from nausea during the first cycle of cisplatin-based chemotherapy. In a subsequent trial, single-dose intravenous fosaprepitant (150 mg) given with ondansetron and dexamethasone was noninferior to standard 3-day oral aprepitant in preventing CINV during OP and DP. In women receiving cyclophosphamide/anthracycline-based chemotherapy for breast cancer, the corresponding figures are 76% and 33%. In patients with breast cancer treated with anthracycline plus cyclophosphamide chemotherapy and receiving the same antiemetic prophylaxis for acute emesis, dexamethasone was not superior to aprepitant but instead had similar efficacy and toxicity in preventing delayed emesis.

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

References:

1. www.mascc.org
2. Keith B.: Systematic review of the clinical effect of glucocorticoids on non-hematologic 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 Guidelines

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

Antiemetische Prophylaxe gemäß MASCC- und ASCO-Guidelines
[ PDF-Datei (auf www.krebsgesellschaft.de) ]
Kurzgefasste interdisziplinäre Leitlinie 2008 der Deutschen Krebsgesellschaft, die unter der Verantwortung der ASO bzw. ASORS erstellt wurde.
Supportive Therapie: Antiemetics (18-19/23)

No further information

No references
Analgesia (20/23)

No further information

References:

Relevant guidelines

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

Schmerztherapie bei Tumorerkrankungen http://www.krebsgesellschaft.de/download/ll_n_02.pdf
Diarrhea (21/23)

No further information

References:

Relevant Guidelines


**Constipation (22/23)**

*Further information:*

Constipation is not infrequently encountered during chemotherapy. Particularly around the time in autumn and winter, when indoor heating begins and air humidity is consequentially reduced. Sufficient fluid uptake should be encountered by treating health care providers. Opioid therapy usually results in constipation and regular digestion should always be aimed at.

A Cochrane meta-analysis investigated differential efficacy of different agents, the authors concluded, that „The findings of our work indicate that Polyethylene glycol is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products. On subgroup analysis, this is seen in both adults and children, except for relief of abdominal pain. Polyethylene Glycol should be used in preference to Lactulose in the treatment of Chronic Constipation.“

More recently, the use of parenteral methylnaltrexone for the management of constipation in palliative care patients was evaluated. Subcutaneous methylnaltrexone; an opioid-receptor antagonist, is now licensed for the treatment of opioid-induced constipation in palliative care when response to usual laxative therapy is insufficient. The authors concluded, that „Here it found that subcutaneous methylnaltrexone is effective in inducing laxation in palliative care patients with opioid-induced constipation and where conventional laxatives have failed. However, the safety of this product is not fully evaluated. Large, rigorous, independent trials are needed.“

*References:*


Further information

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

References:

Breast Cancer: Specific Situations
Breast Cancer:
Specific Situations

- **Versions 2005-2015:**
  Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Rody / Scharl / Schneeweiss / Solomayer

- **Version 2016:**
  Harbeck / Thomssen
Breast Cancer: Specific Situations

- Young patients
- Pregnancy-associated BC
- Elderly patients
- Male patients
- Inflammatory BC
- Occult Primary, CUP (Carcinoma of unknown primary)
- Paget´s disease
- Malignant Phyllodes Tumor
- Sarcomas
# Breast Cancer in Young Women ≤ 35 Years

- Aggressive biological behavior: 2a B
- Benefit from chemotherapy: 1b A ++
- Benefit from endocrine therapy: 1b A ++
- Endocrine therapy (TAM), if possible 5-10 y: 1b B ++
- Benefit from HER2 targeted therapy: 2b B ++
- Benefit from CT induced temporary amenorrhoea: 2b B +/-
- GnRHa as ovarian protection 2 weeks prior to CT: 1b B +/-
- Surgery like ≥ 35 y (in particular BCT): 2b B +
- Stage II–III benefit from PMRT: 2b C +
- Genetic and fertility counseling: 2b B ++
Breast Cancer During Pregnancy* or Breast Feeding

- Breast imaging & biopsy like in non-pregnant
- Staging: ultrasound, chest X-ray if indicated
- Surgery like in non-pregnant patients
- Sentinel node excision (technetium only)
- SLNE during 1st trimester
  - Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs
  - Blue dye (has not been tested in pregnant animals or humans)

* Participation in register study recommended
Breast Cancer During Pregnancy*

- 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

Radiation therapy during pregnancy: 4 C -
(Neo-)adjuvant chemotherapy only after first trimester: ++
Anthracyclines: AC, EC: 2b B ++
Taxanes: 2b B +
MTX (e.g. CMF): 4 D --
Endocrine treatment: 4 D --
HER2-neu targeted treatment: 3a C --
Bisphosphonates, denosumab: 4 D -

* Participation in register study recommended
Breast Cancer During Pregnancy*

- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)
  - Oxford / AGO LoE / GR: 2b C ++
- Termination of pregnancy does not improve maternal outcome
  - Oxford / AGO LoE / GR: 3b C
- Delivery mode like in healthy women, avoid delivery ≤3 weeks from prior chemotherapy
  - Oxford / AGO LoE / GR: 4 C ++
- If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities
  - Oxford / AGO LoE / GR: 5 D ++

* Participation in register study recommended
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
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 standard
  - Surgery similar to „younger“ age
  - Endocrine treatment (endocrine resp.)
  - Chemotherapy (standard regimens)
    - < 70 years
    - > 70 years (especially N+, ER/PgR-)
- Radiotherapy
  - Hypofractionation or sole IORT / IOERT
- Omit radiotherapy after BCT in low risk with endocrine treatment**
- Trastuzumab

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical geriatric assessment</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Treatment according to standard</td>
<td>2a C ++</td>
</tr>
<tr>
<td>Surgery similar to „younger“ age</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Endocrine treatment (endocrine resp.)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Chemotherapy (standard regimens)</td>
<td>1a A +</td>
</tr>
<tr>
<td>&lt; 70 years</td>
<td>2a C +*</td>
</tr>
<tr>
<td>&gt; 70 years (especially N+, ER/PgR-)</td>
<td>1b B +</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>AGO 1b A +</td>
</tr>
<tr>
<td>Hypofractionation or sole IORT / IOERT</td>
<td>DEGRO 1b A +/-</td>
</tr>
<tr>
<td>Omit radiotherapy after BCT in low risk with endocrine treatment**</td>
<td>2b C +</td>
</tr>
</tbody>
</table>

*Study participation recommended

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

Different interpretation of published data by AGO and DEGRO
Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

- Reduced standard treatment

- Options extrapolated from trials in elderly:
  - No breast surgery
    - (consider endocrine options)  
    - 2b C +
  - No axillary clearing (≥ 60 y, cN0, rec.-pos)  
    - 2b B +
  - No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)  
    - 1b B ++
  - Hypofractionated radiotherapy or
    IORT / IOERT as sole radiotherapy modality  
    - 1b B +
  - No chemotherapy if >70 years and negative
    risk-benefit analysis  
    - 2b C +
Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

Diagnosis 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)
- Genetic counselling without affected relatives

Screening for 2nd malignancies
according to guidelines

*Participation in register study recommended
# Male Breast Cancer: Systemic Therapy

**Adjuvant chemotherapy as in women**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>2a B ++</td>
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**HER2-targeted therapy**

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

**Endocrine therapy**

- **Tamoxifen**
  | Oxford / AGO LoE / GR |
  | 2b B ++               |

- Aromatase inhibitors (adjuvant)
  | Oxford / AGO LoE / GR |
  | 2b B -*               |

- Aromatase inhibitors (metastatic BC)
  | Oxford / AGO LoE / GR |
  | 4 C +/-               |

- GnRHa and AI (metastatic BC)
  | Oxford / AGO LoE / GR |
  | 4 C +*                |

- Fulvestrant (metastatic BC)
  | Oxford / AGO LoE / GR |
  | 4 C +/-               |

**Palliative chemotherapy as in women**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>4 C ++</td>
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</table>

*Participation in register study recommended*
Inflammatory Breast Cancer (IBC, cT4d)

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) 2b B ++
- Staging 2c B ++
- Skin punch biopsy (at least 2; detection rate < 75%) 2c B +
- Preoperative chemotherapy 2c B ++
  - Regimens as in non-inflammatory BC: anthracycline and taxane-based 2b B ++
  - In HER2-pos. BC, addition of trastuzumab 2b B ++
  - In HER2-pos. BC, addition of trastuzumab & pertuzumab 2b B ++
  - In HER2-neg. addition of bevacizumab 2b C +/-
- Mastectomy after chemotherapy 2c B ++
  - Breast conserving therapy in case of pCR 2b C +/-
  - Sentinel excision only 3b C - -
- Radiotherapy (PMRT) 2c B ++
- Postoperative systemic therapy as in non-inflammatory BC 4 C ++
## Benefit from Trimodal Treatment in Inflammatory Breast Cancer

### Median survival probability

<table>
<thead>
<tr>
<th>Treatment</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>

### Overall survival-probability (OS)

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<tr>
<th>Treatment</th>
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<td></td>
</tr>
</tbody>
</table>

### Multivariate analysis of OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery &amp; chemotherapy &amp; RT (trimodal therapy)</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Surgery &amp; chemotherapy</td>
<td>1.64</td>
<td>1.46 to 1.84</td>
</tr>
<tr>
<td>Surgery &amp; radiotherapy</td>
<td>1.47</td>
<td>0.96 to 2.24</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>2.28</td>
<td>1.80 to 2.89</td>
</tr>
</tbody>
</table>

Axillary Metastasis in Carcinoma of Unknown Primary (CUP)

- Mammography / Breast ultrasound
- Breast MRI
- Staging (CT thorax / abdomen, thyroid sonography, ENT investigation)
- PET / PET-CT
- Gene expression profiling (e.g. CupPrint™)
- ER, PgR, HER2
- Axillary dissection
- Systemic treatment according N+ tumor
- Mastectomy if breast MRI is negative
- Breast irradiation if breast MRI is negative
- Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LOE/GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography / Breast ultrasound</td>
<td>3 B ++</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>3 B ++</td>
</tr>
<tr>
<td>Staging (CT thorax / abdomen, thyroid sonography, ENT investigation)</td>
<td>3 B ++</td>
</tr>
<tr>
<td>PET / PET-CT</td>
<td>3b B +/-</td>
</tr>
<tr>
<td>Gene expression profiling (e.g. CupPrint™)</td>
<td>2c B +/-</td>
</tr>
<tr>
<td>ER, PgR, HER2</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Axillary dissection</td>
<td>3a C ++</td>
</tr>
<tr>
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</tr>
<tr>
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<td>3a C -</td>
</tr>
<tr>
<td>Breast irradiation if breast MRI is negative</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)</td>
<td>3b B +</td>
</tr>
</tbody>
</table>
Paget’s Disease of the Breast

- Histological verification
- Mammography, sonography
  - MR of the breast if other imaging negative
- Paget’s disease with underlying disease (e.g. invasive breast cancer, DCIS)
  - Therapy according to standard of the underlying disease
  - Surgery must achieve R0
  - Wide excision (like DCIS) + radiotherapy
- 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>Procedure</th>
<th>LOE</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological verification</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Mammography, sonography</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>MR of the breast if other imaging negative</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Paget’s disease with underlying disease</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Therapy according to standard of the underlying disease</td>
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<td></td>
</tr>
<tr>
<td>Surgery must achieve R0</td>
<td>1c</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Wide excision (like DCIS) + radiotherapy</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<td>Isolated Paget’s disease of the NAC:</td>
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<td>Surgery must achieve R0</td>
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<td>++</td>
</tr>
<tr>
<td>Surgical resection only, no adjuvant radiotherapy</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Sentinel-node excision (SNE)</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>
Malignant and Borderline Phyllodes Tumor

- Complete (wide) local excision or MRM: 2b B ++
- SNE / Axillary dissection in cN0: 4 C - -
- Staging: 5 D +/-
- Systemic adjuvant therapy (chemo, endocrine): 4 C - -
- Adjuvant radiotherapy: 4 C - -
  - If \( T \geq 2 \) cm (BCT) or \( T \geq 10 \) cm (mastectomy): 2b C +/-
- Treatment of local recurrence
  - R0 resection: 4 C ++
  - Radiotherapy, chemotherapy after R1 resection: 4 C +/-
- Distant metastases (very rare)
  - Treatment like soft tissue sarcomas: 4 C ++
Sarcoma / Angiosarcoma of the Breast  
(Note: very aggressive!)

### Treatment of Primary Disease:

- **Mammography, sonography to determine extent of disease**
- **Preoperative MRI to determine the extent of disease**
- **Diagnosis by core biopsy**
- **Diagnosis by FNB**
- **Staging (CT thorax & abd.; angiosarcoma: MRI brain)**
- **Prognostic factors: size, grade, margins**
- **Surgery with wide clear margins**
  - Breast-conserving therapy if feasible
- **Axillary dissection if cN0**
- **Adjuvant chemotherapy, radiotherapy**
  - Adjuvant chemotherapy (anthracycline-based), radiotherapy if high risk (grade II-III, size > 5 cm, R1)
- **Regional hyperthermia* (to improve local control and DFS in angiosarcoma) plus chemotherapy and/or radiotherapy**

*Therapy in specialized centres recommended*
Sarcoma / 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)
- Trabectidin (after anthracycline / ifosfamide failure in leiomyosarcoma)

Oxford / AGO LOE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Radiotherapy, chemotherapy</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>after R1 resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment like soft tissue sarcomas</td>
<td>4</td>
<td>C</td>
</tr>
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<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Antiangiogenic treatment</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>(e.g. in angiosarcoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trabectidin (after anthracycline / ifosfamide failure in leiomyosarcoma)</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
Breast Cancer: Specific Situations (2/20)

Further information:

Update January 2016 – Thomssen / Harbeck
Update January 2015 – Solomayer / Harbeck
Update January 2014 – Fehm/Schneeweiss
Update January 2013 – Fersis/Friedrich
Update January 2012 – Lux/Lück
Update Februar 2011 – Janni/Huober
Update Januar 2010 – Mundhenke/Rody

Screened data bases:
Cochrane data base (2012),
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 (3/20)

No further information

References:

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

**Further information:**

Breast cancer in young women is rare and probably a specific entity of high risk for recurrence. Therefore chemotherapy is almost always indicated. Radiotherapy seems to deliver additional benefit. Treatment with tamoxifen of up to ten years is beneficial. It could be demonstrated that therapy induced amenorrhea might be of some benefit in premenopausal women but if this is especially true for pts<35 years has not been proven.

Counselling for fertility protection should be offered and the patient needs to be informed about the possibility of compromised ovarian function due to adjuvant chemo- or endocrine therapy. In Germany, the FERTIPROTECT Project is a platform to gain information how and where to get information.

**International Guidelines:**

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

**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 (5/20)

Further information:

Study link:
http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft.html

The individual breast cancer risk is strongly influenced by endocrine factors. Early menarche, late menopause, low number of children, short nursing periods, and increasing age at first birth are significant risk factors. The life style of the industrialized western world is thus causing an increase in breast cancer incidence.

Moreover, breast cancer incidence is also increasing with age. Pregnant breast cancer patients have an average age of about 32-38 years. Given the increasing average age of pregnant women, the co-incidence of a breast cancer diagnosis with the patient also being pregnant or nursing is becoming more frequent. This fact urgently needs to be acknowledged and accepted by physicians since the diagnosis of breast cancer is frequently being delayed in pregnancy. The average time interval between first symptoms and a definite diagnosis is about 5-15 months. Thus, the diagnosis is typically made at a later stage than outside of pregnancy. This delayed diagnosis is most likely one of the main reasons for the fact that overall survival of pregnant breast cancer patients is worse than that of non-pregnant breast cancer patients even though their stage-adapted prognosis is similar. As a consequence, we not only recommend that pregnant or nursing women need to examine their breast on a regular basis but also that clinical examination of breasts and loco-regional lymph nodes should be part of routine medical care during pregnancy and nursing period.

Another reason for the delayed diagnosis next to “simply not thinking about it” is the reluctancy to order appropriate imaging and diagnostic test during pregnancy. Pregnancy or nursing period are no reason for delaying appropriate diagnostic work-up of a suspicious lesion. The same imaging techniques as in non-pregnant women are available. Breast ultrasound will not harm the fetus. Moreover, mammography can also be used if needed, since the danger of too much radiation for the fetus can be overcome by appropriate protective measures. MRI does not have the danger of radiation but experiences with pregnant breast tissue is limited and interpretation may be difficult. Moreover, the position in the MRI may not be acceptable for most pregnant women. Thus, there is no reason to replace an indicated mammography by an
MRI in pregnant patients. Physiological changes in pregnant or nursing breasts cause an increased false-positive rate in imaging procedures. Thus, in pregnant or nursing women, every suspicious palpable tumor definitely needs to be submitted to a histological diagnosis. As in non-pregnant patients, this can be done by minimal invasive techniques such as core or vacuum biopsies under local anesthesia. An open biopsy is only indicated in situations where minimal invasive procedures may not allow a definite diagnosis. In addition, pregnant women as well as their physicians may be more reluctant towards an open biopsy than towards a minimal invasive procedure, thus increasing again the danger of a delay in diagnosis. It is important to make the pathologist aware of the concurrent pregnancy or nursing period in order to avoid pregnancy-associated diagnostic histological changes to cause any diagnostic difficulties or even false-positive findings.

After diagnosis, therapy recommendations follow treatment outside of pregnancy with a few modifications: Therapeutic radiation of the breast is contraindicated during pregnancy so that a mastectomy would theoretically be the surgical method of choice. However, since adjuvant chemotherapy may be indicated in most cases anyway, the beginning of a radiation therapy may automatically be delayed by a few months thus allowing the pregnancy to reach (almost) full term by the end of chemotherapy. Thus, after delivery, radiation therapy is of course possible and thus breast conserving therapy is a valid option in breast cancer during pregnancy.

In general, chemotherapy can only be applied after the 12th week of pregnancy, i.e. after organogenesis. After the first trimester, chemotherapy does not cause an increased rate of malformations. Yet, there is an increased risk for growth retardation, premature labour, premature delivery, and intrauterine fetal death. Little is known about gonade development of and about the risk for malignancy in the children who were subjected to chemotherapy while still in utero. Indication for chemotherapy follows the guidelines for non-pregnant patients. Yet, one has to consider the individual teratogenic potential of the different chemotherapeutics and plan the delivery date accordingly. Among the most frequently used chemotherapeutics in breast cancer, antimetabolites such as methotrexate (or 5-fluorouracil) should not be used due to their teratogenic potential. For anthracyclines, there is no evidence for major complications. FEC, EC and Epi weekly are safe combinations. Undertreatment should be avoided. There is growing evidence that the use of taxanes is safe. So far, no major complications have been reported. The same is probably true for vinorelbine. Which is possible cytotoxic agent in pregnant metastatic breast cancer patients. Dose-dense chemotherapy does not appear to increase the risk of fetal or maternal complications, but is not recommended at the moment. In conclusion, pregnancy is not a reason for withholding an indicated chemotherapy – the timing however, should take the delivery date into account. Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot be recommended.
Results of studies of bisphosphonates in pregnant animals have shown maternal toxicity, fetal underdevelopment, embryolethality, hypocalcaemia and skeletal retardation, so that bisphosphonates are contraindicated in pregnancy. The delivery should not be planned for the immediate three weeks following a chemotherapy cycle, since maternal side effects (e.g. fatigue, hematotoxicity) may increase the maternal risk for delivery-associated complications. Moreover, the placental excretion function disappears after delivery and the newborn may not be able to metabolize potential chemotherapy remainders.

Prognosis is not improved by cessation of nursing. However, nursing should be stopped before surgery on order to reduce volume of the breast and its blood flow. Moreover, nursing is not recommended during chemotherapy due to excretion of many chemotherapeutics into the milk.

There is neither evidence of direct damage to the fetus due to breast cancer nor of metastases into the fetus. Yet, rare placental metastases have been described.

Termination of pregnancy does not improve the prognosis of the breast cancer and thus is not considered a therapeutic option. Yet, depending on gestational age, termination may be considered if therapy options for the mother are severely compromised by the pregnancy.

Diagnosis of a malignancy during pregnancy causes extreme burden and conflicts for the pregnant women and their families touching on emotional, religious, social and ethical aspects next to medical issues. Most pregnant cancer patients want to “live long enough to see their child grow up”. Thus, decisions about continuing the pregnancy and about treatment should not only consider medical arguments but also take psychological as well as emotional needs of the pregnant patient into account.

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 (6/20)

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

10. 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 (7/20)

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
**Pregnancy Associated Breast Cancer: Outcome (8/20)**

*Further information:*

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

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

*References:*

*In general*


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


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

9. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19: 1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).

**Review articles**

Geriatric Assessment (9/20)

Further information:

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

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 (11/20)

Further information:

Frailty is a factor that is crucial in modern times for assessing older patients who are fit to undergo more invasive/aggressive management. The presence of multiple co-morbidities also affects outcome of surgery and/or adjuvant treatment for older breast cancer patients and can increase the risk of death from causes other than breast cancer. There thus may circumstances where non-operative therapies or even no treatment may be considered preferable due to these patients’ factors and evaluations.

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, Rec pos)


Statement: No radiotherapy (≥ 70 y, pT1, pN0, Rec pos)


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

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 \textit{BRCA1} and \textit{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 \textit{BRCA2} than \textit{BRCA1} families. In a southern Californian population, there were no \textit{BRCA1} mutations in 54 patients with male breast cancer, whereas there was a \textit{BRCA2} mutation in two (4%) patients. In 94 patients in the UK there were no germline \textit{BRCA1} mutations, but five (6%) patients had \textit{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 \textit{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


Further information:

Adjuvant chemotherapy: LoE: 4; References 1-4 (retrospective analysis, case series)
Adjuvant CMF chemotherapy was associated with an improvement in disease-free and overall survival. Only 50% of the patients (N=24) actually received the planned 12 cycles of CMF due to side effects.

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)
Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free survival and OS. Tamoxifen is well tolerated with the most common side effects being: Loss of libido (29%), weight gain (25%), heat flushes (21%), mood changes (21%), and depression (17%). The use of aromatase inhibitors has to be regarded as an experimental therapy at present. Due to the different physiological prerequisites for estrogen production in men and women, the effect of lowering serum estrogen levels in men has not yet been scientifically validated. Comparing adjuvant therapy with tamoxifen to aromatase inhibitors for 257 male breast cancer patients the overall survival was significantly better after treatment with tamoxifen.

Palliative endocrine therapy: LoE: 4; References 1-4 (retrospective analysis, case series)
In the metastatic setting there are data on achievement of stable disease being the maximum response to AI. Case reports do exist for anastrozol, letrozol and also fulvestrant.

Because of the low evidence level for the treatment of male breast cancer we believe that new studies should not exclude male patients. International registries should be participated in.

References:

Statement: Adjuvant Chemotherapy


Statement Trastuzumab


Statement endocrine therapy


Statement palliative chemotherapy

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

*Further information:*

There is little information on inflammatory breast cancer (IBC) alone. Most retrospective analysis focus on T4 carcinomas without separating T4d cancer. Primary IBC is probably a distinct biological entity compared to non IBC. Prospective randomised studies for the diagnosis and treatment of patients suffering from inflammatory breast cancer are still missing. The matter of current updates is aiming on the definition, including the confirmation of an invasive carcinoma as well as clinical signs of the skin affection ≥ 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 bevacizumab


Statement: Mastectomy after chemotherapy


Statement: Sentinel lymph node


Statement: Radiotherapy


Statement: Postoperative systemic therapy as in non-inflammatory BC


Reviews

Benefit from Trimodal Treatment in Inflammatory Breast Cancer (15/20)

Further information and references:

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

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

Further information:

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

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

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


Statement: Mammography / Breast ultrasound/ Breast MRI

1. Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8

Statement: Staging


Statement: PET

5. Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85

Statement: Gene expression profiling

2. Gauri et al., JCO, 26:4442-8, 2008;
3. Horlings et al., JCO, 26: 4435-4441, 2008

**Statement: ER, PR, HER2**


**Statement: Axillary dissection**


**Statement: Systemic treatment according N+ tumor**

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


Statement: Breast irradiation if breast MRI is negative

Paget’s Disease of the Breast (17/20)

Further information:

Paget’s disease is a rare disease, therefore separate literature is scarce.

References:

Statement: MR of the breast if other imaging negative


Statement: Wide excision (like DCIS) + radiotherapy:


Statement: Sentinel-node excision (SNE)

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


Statement: Isolated Paget’s disease of the NAC (<5%): surgical resection only, no adjuvant radiotherapy

Review:
Malignant and Borderline Phyllodes Tumor (18/20)

Further information:

Phyllodes tumors (PTs) of the breast are biphasic neoplasms composed of epithelium and a spindle-cell stroma. Currently, PTs are classified as benign, borderline, or malignant based on histopathologic features. The presence of pain (P = 0.03), tumor size > 5 cm (P = 0.005), postmenopausal status (P < 0.04), heavy cellular pleomorphism (P = 0.007), high mitotic activity (P = 0.002), tumoral grade (P = 0.006) and metastasis (P < 0.00001) were prognostic factors of poor survival. (Roa JC: Pathol Int. 2006 Jun;56(6):309 / Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11).

However, histologic classification does not always predict outcome. Stromal c-Kit positivity and epithelial endothelin 1 negativity are more often associated with malignant PTs; however, only positive margin status is significantly associated with tumor behavior (Esposito NN: Arch Pathol Lab Med. 2006 Oct;130(10):1516-21).


References:

In general


Statement: Core biopsy

1. Hyun Kyung Jung, Hee Jung Moon, Min Jung Kim, Eun-Kyung Kim Benign core biopsy of probably benign breast lesions 2 cm or larger: correlation with excisional biopsy and long-term follow-up. Ultrasonography 2014;33:200-205

Statement: Diagnosis


Statement: Complete (wide) local excision or MRM (LoE: 2c):
References 1-4 (retrospective analysis, case reports)

1. Macdonald OK: Cancer. 2006 Nov 1;107(9):2127-33

Statement: SNE / Axillary dissection in cN0 (LoE: 4):
References 1-3 (retrospective analysis, case reports)

2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94

Statement: Staging (LoE 5 D AGO+/-)

Note: In malignant phyllodes tumours, the risk of developing of metastases has been described between 10% and 35%, mean 17%; some authors with larger series (Belkacemi et al.2008) observed only 3.4% in their series. Therefore, patients with benign phyllodes tumours do not need extensive staging diagnostics, patients with malignant phyllodes tumours having residual tumour after surgery or having a high proliferation rate (>5 mitotic counts) an higher rate of recurrences has been observed, however, most often as local recurrences. In benign phyllodes tumours, distant metastases are unknown, whilst in borderline lesions also distant metastases may occur, but less frequent than in malignant disease. In summary, as in breast cancer, clinical staging may be worthwhile, a additional impact by regular imaging including PET and MRI in the follow-up has not been shown.

2. Shingo Baba1, Takuro Isoda, Yasuhiro Maruoka, Yoshiyuki Kitamura, Masayuki Sasaki, Tsuyoshi Yoshida, and Hiroshi Honda Diagnostic and Prognostic Value of Pretreatment SUV in 18F-FDG/PET in Breast Cancer:


Statement: Systemic adjuvant therapy/ Chemotherapy (LoE: 4):

References 1 (cohort studies, case reports)


Endocrine therapy (LoE: 5)


Statement: Adjuvant radiotherapy: Radiotherapy after R0 (LoE: 4):

References 1-3 (retrospective analysis, cohort studies)


2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94


Statement: Adjuvant radiotherapy, if $T \geq 2\text{cm (BCT)}$ or $T \geq 10\text{cm (mastectomy)}$


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

1. Soumarova R: Arch Gynecol Obstet. 2004 May;269(4):278-81

Statement: Radiotherapy, chemotherapy after R1 resection

Statement: Distant metastases (very rare) => Treatment like soft tissue sarcomas

Sarcoma / Angiosarcoma of the Breast (19/20)

Further information:

The management of angiosarcomas at different sites were recently summarized in review. Radical surgery with complete RO resection is the primary treatment of choice. Because of the high risk of local recurrence radiotherapy should be considered. In view of the risk of metastatic disease there is a rationale for adjuvant chemotherapy. However up to now there is no convincing evidence to support the use of adjuvant chemotherapy. Active agents in metastatic angiosarcoma are anthracylines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

Reference:

In general


Primary angiosarcoma (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent. Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm. The imaging features of AS are non-specific in mammography and up to 33% are undetectable. On ultrasound examination, there is a heterogenous
echogenicity with hyperechoic areas without acoustic shadowing. The most useful imaging technique to determine the extent of AS is breast MRI that shows hypervascular, heterogeneous masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images.

Histologic grading is important for the assessment of prognosis with the 5-year recurrence free survival of 76% for low grade AS and 15% for high grade AS but reported survival data differ widely. The role of adjuvant radiotherapy and chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with anthracycline-ifosfamide or gencitabine-taxane. Four had complete response and 10 a partial response (48% overall response rate), but there was no difference in DFS or OS between patients who received no adjuvant treatment. In an older series, 20% of low, 40% of intermediate and 71% of high-grade lesions recurred following chemotherapy. In contrast 27%, 40% and 100% of low, intermediate and high-grade lesions recurred in patients who did not receive adjuvant chemotherapy. Therefore, the role of adjuvant chemotherapy for AS of the breast remains unclear.

Secondary angiosarcoma (AS) occurs following radiotherapy after breast conserving therapy or after chest wall irradiation after mastectomy. Therefore the term radiotherapy-associated angiosarcoma may also be used. Another, much rarer occurrence of post-treatment angiosarcoma is in the upper limb following longstanding lymphoedema after mastectomy, with or without radiotherapy. This has also been called Steward-Treves syndrome and is not radiotherapy-associated and therefore not considered here.

The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation.

Current data show that not the type of operation in the case of sarcomas of the breast, particularly the angiosarcoma, a serious disease that could appear 10-15 years after radiation therapy, but factors such as size, grading and especially the adequate safety margins are important diagnostic factors. Thus, breast conserving surgeries could be performed with larger safety margins, if feasible and after given consent of the associated risk [AGO 4/C/++] (Al-Benna et al. 2010; Voutsadakis et al., 2011). It should be diagnosed through punch biopsy not via fine-needle biopsy. Postoperatively an anthracycline-based chemotherapy in combination with radiotherapy could be considered particularly in high-risk situations [AGO 4/C/+/-] (Barrow et al., 1999). If metastases have already occurred, paclitaxel as well as liposomal doxorubicin should be applied especially in patients with angiosarcoma. In case of unsuccessful treatment with anthracyline and ifosfamid, trabectedin could be used in patients suffering from leiomyosarcoma [AGO 2b/B/+] (Schöffski et al., 2011).


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

No further information

References:

Hyperthermia:

Breast Cancer
Follow-Up
Breast Cancer Follow-Up

- **Versions 2002–2015:**
  Bauerfeind / Bischoff / Blohmer / Böhme / Costa / Diel / Gerber / Hanf / Heinrich / Janni / Kaufmann / Kümmel / Lux / Maass / Möbus / Mundhenke / Oberhoff / Rody / Scharl / Solomayer / Thomssen

- **Version 2016:**
  Huober / Diel
Early detection of curable events

- In-breast recurrence
- Loco-regional recurrence*

Early detection of metastases

- Early detection of symptomatic metastases
- Early detection of asymptomatic metastases

* loco-regional recurrence is associated with higher risk for mortality in node positive, PR negative, younger patients and patients with short time from diagnosis to recurrence
Breast Cancer Follow-Up
Objectives II

- 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 III

- **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)

Oxford / AGO
LoE / GR

5 D ++
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

- General counseling (genetics, HRT, prophylactic surgery, breast reconstruction)

Oxford / AGO
LoE / GR

4 C +
2c B ++
2c C +
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

Oxford / AGO LoE / GR
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

<table>
<thead>
<tr>
<th>Tests</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History (specific symptoms)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Physical examination</td>
<td>1a B ++</td>
</tr>
<tr>
<td>Breast self-examination</td>
<td>5 D +</td>
</tr>
<tr>
<td>Mammography</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Sonography of the breast</td>
<td>2a B ++</td>
</tr>
<tr>
<td>Routine MRI of the breast</td>
<td>3b B +/-</td>
</tr>
<tr>
<td>MRI of the breast in case of inconclusive conventional imaging</td>
<td>3b B +</td>
</tr>
<tr>
<td>Pelvic examination</td>
<td>5 D ++</td>
</tr>
<tr>
<td>DXA-scan at baseline and repeat scan according to individual risk in women with premature menopause or women taking an AI</td>
<td>5 D +</td>
</tr>
</tbody>
</table>

**Notes:**
- **LoE:** Level of Evidence
- **GR:** Grade of Recommendation
- **A:** Strongly recommended
- **B:** Recommended
- **C:** Conditional recommendation
- **D:** Not recommended
- **+/−:** Limited recommendation
Routine Follow-Up Examinations in Asymptomatic Patients

- Routine biochemistry (incl. tumor markers)  
  Oxford / AGO LoE / GR: 1a A -

- Ultrasound of the liver  
  Oxford / AGO LoE / GR: 1a A -

- Bone scan  
  Oxford / AGO LoE / GR: 1a A -

- Chest X-ray  
  Oxford / AGO LoE / GR: 1a A -

- CT of chest, abdomen and pelvis  
  Oxford / AGO LoE / GR: 2a D -

- Detection of isolated / circulating tumor cells  
  Oxford / AGO LoE / GR: 2a D -

- PET  
  Oxford / AGO LoE / GR: 2b B -

- Whole body MRI  
  Oxford / AGO LoE / GR: 2b B -
Early Detection of Potentially Curable Events

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)

Oxford / AGO LoE / GR

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 ca. 1.5; lymphoma RR 7
- Screening for secondary malignancies according to current guidelines ++
- Pelvic examination and PAP smear 5 D ++
- Routine endometrial ultrasound / biopsy 1b B -
# Follow-Up Care for Breast Cancer

**Recommendations for asymptomatic pts.**
(modified ASCO-ACS guidelines 2016, NCCN 1.2016 guidelines and S3 national German guideline 2012)

<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 sono-graphy</td>
<td>BCT**</td>
<td>ipsilat.: every 12 months contralat.: every 12 months</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. Breast Nurses.

- **Duration of follow-up**
  - until 5 yrs
  - until 10 yrs

- **Surveillance by specialized breast nurses**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>until 5 yrs</td>
<td>1c A ++</td>
</tr>
<tr>
<td>until 10 yrs</td>
<td>1c A +</td>
</tr>
<tr>
<td>Surveillance by specialized breast nurses</td>
<td>2b B +/-*</td>
</tr>
</tbody>
</table>

*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

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

1. Expert opinion Organkommission

Statement: Monitoring of compliance

1. Hershman DL et al., SABCS, 2010
3. Neven P, Markopoulos C, Tanner MME et al.: The Impact of Educational Materials on Compliance and Persistence with Adjuvant Aromatase Inhibitors: 2 Year Follow-Up and Final Results from the CARIATIDE Study. SABCS 2011 [P5-16-02].
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:

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: Dexa 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

1. Otto Metzger-Filho et al. Patterns of Recurrence and Outcome According to Breast Cancer Subtypes in Lymph Node–Negative Disease: Results From International Breast Cancer Study Group Trials VIII and IX, JCO September 1, 2013 vol. 31 no. 25 3083-3090
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

1. Rieck GC, Lim K, Rogers MT: Screening for familial ovarian cancer--management and outcome of women with moderate to high risk of developing ovarian cancer. Int J Gynecol Cancer. 2006 Jan-Feb;16 Suppl 1:86-91

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. Breast Nurses. (15/16)

No further information

References:

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

No further information

References:


2. Otto Metzger-Filho et al., Patterns of Recurrence and Outcome According to Breast Cancer Subtypes in Lymph Node–Negative Disease: Results From International Breast Cancer Study Group Trials VIII and IX, JCO September 1, 2013 vol. 31 no. 25 3083-3090
Loco-regional Recurrence
Loco-regional Recurrence

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

<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>
</tr>
<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**
- **Reassessment of ER, PR, HER2**
- **Complete re-staging**

### Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Description</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>AGO GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Biopsy</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Reassessment of ER, PR, 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
- Number of involved lymph nodes
- Omitting adjuvant radiotherapy (if indicated)
- Extensive intraductal component
- Vessel invasion
- Triple negative and HER2 / HR- vs. HR+
- Grading (G3 vs. G1)
- Elevated proliferation markers: partic. Ki67;
- pT (> 2 vs. ≤ 2cm)
  - * node negative
- pN (N1 vs. N0)
- Inflammatory breast cancer
- Medial tumor localisation (vs. central/lateral)
- Obesity (Body mass index)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>1a</td>
</tr>
<tr>
<td>Positive microscopic margins</td>
<td>1a</td>
</tr>
<tr>
<td>Number of involved lymph nodes</td>
<td>1a</td>
</tr>
<tr>
<td>Omitting adjuvant radiotherapy (if indicated)</td>
<td>1a</td>
</tr>
<tr>
<td>Extensive intraductal component</td>
<td>1b</td>
</tr>
<tr>
<td>Vessel invasion</td>
<td>1b</td>
</tr>
<tr>
<td>Triple negative and HER2 / HR- vs. HR+</td>
<td>2a</td>
</tr>
<tr>
<td>Grading (G3 vs. G1)</td>
<td>1b*</td>
</tr>
<tr>
<td>Elevated proliferation markers: partic. Ki67;</td>
<td>2b</td>
</tr>
<tr>
<td>pT (&gt; 2 vs. ≤ 2cm)</td>
<td>1b*</td>
</tr>
<tr>
<td>* node negative</td>
<td>1a</td>
</tr>
<tr>
<td>pN (N1 vs. N0)</td>
<td>1a</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>2b</td>
</tr>
<tr>
<td>Medial tumor localisation (vs. central/lateral)</td>
<td>4</td>
</tr>
<tr>
<td>Obesity (Body mass index)</td>
<td>1a</td>
</tr>
</tbody>
</table>
### Metaanalysis: TNBC and Local Recurrence

Wang et al., Surg Oncol 2013 (Epub)

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

<table>
<thead>
<tr>
<th></th>
<th>BCT</th>
<th>vs.</th>
<th>ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.75 (0.65-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>0.68 (0.60-0.76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>other subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>1.88 (1.58-2.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>2.12 (1.72-2.62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>HER2-subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.69 (0.53-0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</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

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

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

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

Result:
HR-positive tumors exhibit the lowest rate of local recurrence.
Loco-regional Recurrence
Prognostic / Predictive factors

Parameters in local recurrence to define risk for re-recurrence

- Tumor size
- Multifocality
- Localisation

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

- Early (<2-3 yrs.) vs. late recurrence
- LVSI/Grade/ERneg/positiv margin

Predictive factors for treatment considerations

- HER2
- ER and PgR
Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence


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) 3b B ++
- Re-BCS with tumor-free margins 3b C +/-
- Axillary intervention after prior AxDiss if cN0 4 C -
- SNE after prior SNE if cN0 1b B +/-
- Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial) 5 D +

*If no sentinel lymph node can identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended
Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

- **Curative situation: R0-resection**
  - Oxford LoE / AGO LoE: 2b A ++

- **Palliative situation: Resection of deep parts of the chest wall**
  - Oxford LoE / AGO LoE: 5 D +/-

- **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**
  - Oxford LoE / AGO LoE: 5 D +
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
  - LoE/B: 2b B ++
- Chemotherapy (consider neoadjuvant)
  - LoE/B: 2b B +
- In case of HER2 positive disease
  - Chemotherapy + HER2 targeted therapy
  - LoE/D: 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)

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy in endocrine responsive tumors</td>
<td>2b</td>
<td>B ++</td>
</tr>
<tr>
<td>Chemotherapy (pre- or postoperatively)</td>
<td>2b</td>
<td>B ++</td>
</tr>
<tr>
<td>HER2-targeted therapy in HER2-overexpressing tumors (with chemotherapy)</td>
<td>5</td>
<td>D ++</td>
</tr>
</tbody>
</table>
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%)
## Chest-Wall Recurrence after Mastectomy

- **If no prior postmastectomy radiotherapy**
  - Curative situation: irradiation of the chest wall +/- regional lymph nodes
  
<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

- Re-irradiation (chest wall + hyperthermia)
  
<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

## Axillary recurrence

**Irradiation of axilla after R0-surgery**

- No prior adjuvant irradiation of the axilla
  
<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>C</td>
</tr>
</tbody>
</table>

- Adjuvant irradiation of the axilla
  
<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>D</td>
</tr>
</tbody>
</table>
Loco-Regional Recurrence
Treatment Options
in Non Curative Cases

- Topical chemotherapy (miltefosine) 3b C +
- Concomitant radio-chemotherapy 3b C +
- Hyperthermia (in centers listed on DKG website)
  - In combination with radiotherapy 1b B +
  - In combination with chemotherapy 4 C +/-
- Intra-arterial chemotherapy 4 C +/-
- Photodynamic therapy 4 C +/-
- Electrochemotherapy 3b C +/-
LOCO-REGIONAL RECURRENCE (2/18)

Further information:


Guidelines:


Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms
No references
Loco-regional Recurrence Incidence and Prognosis (3/18)

Further information:

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

References:


**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.

**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:*

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


HER-2 positive breast cancer is associated with an increased risk of positive cavity margins after initial lumpectomy Haixia Jia, Weijuan Jia, Yaping Yang, Shunrong Li, Huiyi Feng, Jieqiong Liu, Nanyan Rao, Liang Jin, Jiannan Wu, Ru Gu, Liling Zhu, Kai Chen, Heran Deng, Yunjie Zeng, Qiang Liu, Erwei Song, and Fengxi Su

HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Jia WJ1, Jia HX, Feng HY, Yang YP, Chen K, Su FX.

**Statement: Grading (G3 vs. G1)**


**Statement: pT (> 2 vs. ≤ 2cm)**


Statement: pN (N1 vs. N0)


Statement: pT (> 2 vs. ≤ 2cm) and Grading (G3 vs. G1) in node negative


Statement: pN (N1 vs. N0)

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

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: number of involved lymph nodes**


**Statement: Medial tumor localisation (vs. central/lateral)**

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: 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. In case no sentinel lymph node can be identified, axillary dissection is not recommended.

**References:**

**Statement: Mastectomy (aim: R0)**

Statement: Re-BCS with tumor-free margins ± flap reconstruction


Statement: disadvantage for overall survival cannot be excluded, poor cosmetic result, impaired local tumor control


Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0


Reoperative Sentinel Lymph Node Biopsy is Feasible for Locally Recurrent Breast Cancer, But is it Worthwhile? Ugras S1, Matsen C1,2, Eaton A3, Stempel M1, Morrow M1, Cody HS 3rd4.

Statement: Palliative surgery in M1-situation

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


Cytotoxic Treatment in pts with Local Recurrent Breast Cancer (14/18)

No further information

No references
Locoregional Recurrence in case R0-resection not likely - Systemic Treatment (15/18)

No further information

References:

Statement: Endocrine therapy in endocrine responsive disease


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

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


**Loco-Regional Recurrence - Treatment Options in Non-Curative Cases (18/18)**

**Further information:**

The combination of chemotherapy and hyperthermia (HT) is a promising approach in the treatment of malignant tumors. Local hyperthermia combined with radiotherapy may be effective in the treatment of locally recurrent breast cancer, especially for previously irradiated cases, where only a reduced total irradiation dose is applicable. Care should be taken to select experienced providers that treat accordingly to recognised guidelines. While the combination of hyperthermia and radiotherapy has been used for several decades and shown its efficacy in prospective randomized trials, the combination of chemotherapy and hyperthermia (HT) has much less intensively been studied in breast cancer. Few recent papers report on trimodal therapeutic attempts: chemotherapy, radiotherapy plus hyperthermia, the additional benefit of chemotherapy is not quite clear.

**References:**

Statement: Topical chemotherapy (miltefosine)


Statement: Concomitant radio-chemotherapy

Statement: Hyperthermia + radiotherapy +/- chemotherapy

11. Linthorst M, Baaijens M, Wijgenraad 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

- **Versions 2003–2015:**
  Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Liedtke / Loibl / Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schneeweiß / Schütz / Stickeler

- **Version 2016:**
  Hanf / Mundhenke
Endocrine Therapy in Metastatic Breast Cancer

Indication

- Oxford LoE: 1a
- GR: A
- AGO: ++

Endocrine therapy represents the first choice for metastatic breast cancer with positive (or unknown) hormone receptor (HR) status.

- Exception: acute life-threatening disease
- Caveat: HR might change during the course of disease. Histology of recurrent site should be obtained whenever possible
Comparison ER/PR and HER2
Metastasis vs. Primary Tumor

Meta-analysis based on 48 (mostly retrospective) analyses:

Pooled discordance proportions were
- 20% (95%CI 16-35%) for ER
- 33% (95%CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Pooled proportions of tumors shifting from positive to negative and negative to positive were
- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2
Endocrine Therapy
General considerations

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

Oxford / AGO LoE / GR
**Endocrine Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer**

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Aromatase inhibitors (3rd gen) **</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Letrozole + Palbociclib</td>
<td>1b B +</td>
</tr>
<tr>
<td>Fulvestrant 500 mg plus Palbociclib</td>
<td>1b B +</td>
</tr>
<tr>
<td>Exemestane + Everolimus</td>
<td>1b A +</td>
</tr>
<tr>
<td>Tamoxifen + Everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>MPA/MA $</td>
<td>1a A +/-</td>
</tr>
<tr>
<td>Fulvestrant 250 mg + Anastrozol</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Estradiol valerate 2-6 mg daily</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>
Therapy Algorithm After Adjuvant Tamoxifen

Fulvestrant 500 mg or Non-steroidal AI 3rd generation or Tamoxifen*

- Exemestane + everolimus
- Fulvestrant 500 mg +/- Palbociclib

Fulvestrant 500 mg +/- Palbociclib

- Exemestane + everolimus
- Tamoxifen

*(after long recurrence-free interval)
Therapy Algorithm After Adjuvant AI

**Short treatment free interval ≤12 months**
- Exemestane + everolimus
  - Tamoxifen

**Long treatment free interval >12 months**
- Fulvestrant 500 mg +/- Palbociclib
  - Exemestane + everolimus
    - Tamoxifen
    - Fulvestrant 500 mg +/ Palbociclib
  - Tamoxifen
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
  - **Oxford / AGO LoE / GR**
  - 2b  B  +

- Bevacizumab plus endocrine treatment as first line therapy for advanced disease
  - 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

Poor efficacy of endocrine therapy alone.

Consider induction chemotherapy + anti-HER2-therapy!
## Combination of Endocrine Treatment with Anti-HER2-Treatment

<table>
<thead>
<tr>
<th>Treatment (no. of pats)</th>
<th>PFS (months)</th>
<th>Response rate (CBR)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + anastrozole vs. anastrozole (n=207)</td>
<td>4.8 vs. 2.4 (5.6 vs. 3.8 with centrally confirmed receptor status)</td>
<td>42.7% vs. 27.9%</td>
<td>28.5 vs. 23.9 mo; n.s.</td>
</tr>
<tr>
<td>Trastuzumab + letrozole vs. letrozole (n=57)</td>
<td>14.1 vs. 3.3</td>
<td>27% vs. 13%</td>
<td>not reported</td>
</tr>
<tr>
<td>Lapatinib + letrozole vs. letrozole (n=219/1286)</td>
<td>8.2 vs. 3.0</td>
<td>48% v 29%</td>
<td>33.3 vs. 32.3 mo</td>
</tr>
<tr>
<td>Lapatinib + fulvestrant vs. fulvestrant (n=146/145)</td>
<td>4.1 vs. 3.8 (HER2-) p: 0.25 5.9 vs. 3.3 (HER2+): 0.53</td>
<td>(CR +PR) 20 vs. 9% p: 0.048</td>
<td>30 vs. 26.4 mo (all), n.s.</td>
</tr>
</tbody>
</table>
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

1b  A  -

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

No further information

No references
Endocrine and “Targeted” Therapy in Metastatic Breast Cancer (3/14)

No further information

References:


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

No further information

References:

Endocrine Therapy  General Considerations (5/14)

No further information

References:

“Aromatase inhibitors (3rd gen) (> non-AI*)”


4. Thuerlimann, B, Robertson, JFR, Nabholtz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole (‘Arimidex’) compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer 2003 39

5. Bonneterre, J, Buzdar, A, Nabholtz, JA, Robertson, JF, Thuerlimann, B, von Euler, M, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


Fulvestran 250 mg (=AI)

1. Howell, A, Robertson, JFR, Quaresma Albano, J, Asegermannova, A, Mauriac, L, Kleeberg, UR, Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment Journal of Clinical Oncology 2002 20

2. Mauriac, L, Pippen, JE, Quaresma Albano, J, Gertler, SZ, Osborne, CK, Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials European Journal of Cancer 2003 39


fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 2008 Apr 1;26(10):1664-70.


**Fulvestrant 500 mg**


**MPA/MA inferior to AI**

5. Goss, PE, Winer, EP, Tannock, IF, Schwarz, LH, Randomized phase III trial comparing the new potent and selective third generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients Journal of Clinical Oncology 1999 17

Comparison of different AI

**Fulvestrant and anastrozol (vs. AI)**


**Letrozole and Palbociclib (vs. Letrozol)**

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

No further information

References:

GnRHa plus Tamoxifen (vs. OFS or Tam)


**Ovarian function suppression (OFS), Tamoxifen**


**GnRHa plus AI (first or second line)**


**GnRHa plus Fulvestrant**


**GnRHa+ Fulvestrant +/- Palbociclib 1b B +**

References:

“"Aromatase inhibitors (3rd gen) (> non-AI*)“


4. Thuerlimann, B, Robertson, JFR, Nabholz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole ("Arimidex") compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer of 2003 39

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   Kaufmann, M, Bajetta, E, Dirix, LY, Fein, LE, Jones, SE, Zilembo, N, Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomised double-blind trial Journal of Clinical Oncology 2000 18

Comparison of different AI


Fulvestrant and anastrozol (vs. AI)


Letrozole and Palbociclib (vs. Letrozol)

Fulvestrant and Palbociclib

Therapy Algorithm after Adjuvant Tamoxifen (8/14)

No further information

No references
Therapy Algorithm after Adjuvant AI (9/14)

*No further information*

*No references*
Endocrine Therapy in Premenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab (10/14)

No further information

References:

2. Bevacizumab plus endocrine treatment as first line therapy for advanced diseasePhase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study.
Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients (12/14)

No further information

References

Anastrozole and trastuzumab


Letrozole and trastuzumab


Letrozole and lapatinib

**Fulvestrant and lapatinib**

Combination of Endocrine Treatment with Anti-HER2-Treatment (13/14)

No further information

References:


Concomitant or Sequential Endocrine-Cytostatic Treatment (14/14)

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 2003–2015:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Möbus / Müller / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thomssen / von Minckwitz

➢ **Version 2016:**
  Thill / Rody
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 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 while on the first 2 years of adjuvant ET,
Or PD within first 6 months of first-line ET for MBC, while on ET

Secondary endocrine resistance:
Relapse while on adjuvant ET but after the first 2 years,
or a relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for MBC, while on ET
# 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 (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 (primary tumor, better metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>bone 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

LoE: 1c  GR: A  AGO: ++

- Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities)
- Assess subjective and objective toxicities, symptoms, and performance status repeatedly
- Use dosages according to published protocols
- Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion might be sufficient. In slowly growing disease, longer intervals are acceptable.
Cytotoxic Therapy
Duration

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 A ++</td>
<td></td>
</tr>
<tr>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>1c A ++</td>
<td></td>
</tr>
</tbody>
</table>
Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends on:

- ER / PR, HER2; combination with biologicals
- Previous treatments (and their toxicities)
- Disease-free interval after end of adjuvant treatment
- Aggressiveness of disease and localization of metastases
- Estimated life expectancy
- Co-morbidities (including organ dysfunctions)
- Patients preference and expectations
MBC HER2-negative/HR-positive Cytotoxic 1st-Line Therapy*

Monotherapy:

- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, mitoxantrone (A)
- Peg. liposomal doxorubicin ($A_{lip}$)
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

Polychemotherapy:

- A + T
- T + gemcitabine after adj. A
- A + C or $A_{lip}$ + C
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3b B +</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b B +</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b B +</td>
</tr>
<tr>
<td>A + T</td>
<td>1b A ++</td>
</tr>
<tr>
<td>T + gemcitabine after adj. A</td>
<td>2b B ++</td>
</tr>
<tr>
<td>A + C or $A_{lip}$ + C</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Paclitaxel + capecitabine</td>
<td>2b B +</td>
</tr>
<tr>
<td>Docetaxel + capecitabine after adj. A</td>
<td>1b A +</td>
</tr>
</tbody>
</table>

*In ER pos. disease only if endocrine therapy is not or not anymore indicated
Taxane-containing Regimens for Metastatic Breast Cancer


See: Forest plot of comparison: I Overall survival, outcome: I.I Overall effect: Taxane-containing regimes vs. not
# MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel q1w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Docetaxel q3w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Docetaxel + Peg-liposomal Doxo</td>
<td>1b</td>
<td>B</td>
<td>+/-</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>
# 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. GemPac)

- Bevacizumab added to first line cytotoxic therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Level</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental therapies within studies</td>
<td>++</td>
<td></td>
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<tr>
<td>Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin (vs. Docetaxel)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Gemcitabine/Cisplatin (vs. GemPac)</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Bevacizumab added to first line cytotoxic therapy</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
### Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>1st line in combination with:</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (q1w)</td>
<td>1b B +</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b B +</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Nab-Pac</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Docetaxel (q3w)</td>
<td>1b B +/-</td>
</tr>
</tbody>
</table>

| Cap+Bev as maintenance after Doc+Bev | 1b B +/- |
| 2nd line as treatment through multiple lines | 1b B +/- |

<table>
<thead>
<tr>
<th>2nd line in combination with:</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxanes</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Gemcitabine or vinorelbine</td>
<td>1b B -</td>
</tr>
</tbody>
</table>
First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + trastuzumab + pertuzumab</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Paclitaxel (wk) + trastuzumab + pertuzumab</td>
<td>2b B +</td>
</tr>
<tr>
<td>Vinorelbine + Trastuzumab + Pertuzumab</td>
<td>3b(^{a}) B +/-</td>
</tr>
<tr>
<td>T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)</td>
<td>2b B +</td>
</tr>
<tr>
<td>1(^{st}) line chemotherapy* + trastuzumab</td>
<td>1b B +</td>
</tr>
<tr>
<td>Trastuzumab mono</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Taxanes + lapatinib</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Taxanes + trastuzumab + everolimus</td>
<td>1b B -</td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
</tr>
</tbody>
</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
- Capecitabine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Taxane + trastuzumab + pertuzumab
- Any other 2nd line chemotherapy* + trastuzumab + pertuzumab
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

*E.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

Oxford / AGO LoE / GR

T-DM 1  1b  A  ++
TBP: 2nd line chemotherapy + trastuzumab  2b  D  +
Capecitabine + lapatinib  1b  B  +
Trastuzumab + lapatinib (HR neg. disease)  2b  B  +
Taxane + trastuzumab + pertuzumab  5  D  +/-
Any other 2nd line chemotherapy* + trastuzumab + pertuzumab  5  D  +/-
Trastuzumab + aromatase inhibitors (if ER+)  3b  B  +
Lapatinib + aromatase inhibitors (if ER+)  3b  B  +
Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

Pretreatment with Trastuzumab

- T-DM 1                   1b A ++
- Capecitabine + lapatinib  1b B +
- Vinorelbine + lapatinib   2b B +/-
- Trastuzumab + lapatinib (HR neg. disease) 2b B +
- Chemotherapy + trastuzumab + („treatment beyond progression“) 2b B +
  - Trastuzumab + pertuzumab 2b B +
  - Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated) 1b B +/-

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen 5 D +

For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above. There is no data for treatment beyond progression for pertuzumab.
Lapatinib in HER2-positive Metastatic Breast Cancer

In combination with

- Trastuzumab for heavily pre-treated pts
- Paclitaxel in 1st line
- Capecitabine in > 2nd line
- Vinorelbine
- AI in ER positive disease
- In patients with brain metastases (radioresistance) in combination with capecitabine

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab for heavily pre-treated pts</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel in 1st line</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Capecitabine in &gt; 2nd line</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>AI in ER positive disease</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>In patients with brain metastases</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

( radioresistance) in combination with capecitabine
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

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

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

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 (3/20)

No further information

References:

Increase


Multiple lines

Endocrine resistance in metastatic breast cancer (4/20)

No further information

References:

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

No further information

References:

CTC monitoring


Cytotoxic Therapy Goals (6/20)

No further information

References:

2. (Sledge et al, 2003).

Combination vs single agent


Metaanalysis

Docetaxel alone or in combination
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.

Cochrane analysis


Single trials:

Combination not superior compared to single agent regimen.


Tailored therapy in MBC

Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.

Cytotoxic and Targeted Therapy (7/20)

No further information

References:

Cytotoxic Therapy Duration (8/20)

Further information:

Consent:
Treatment until progression  6++, 18+, 2+/-,1-
Treatment until best response 1++, 3+, 23+/-,1-
Change to alternative regimen before progression 1++, 0+, 25+/-, 5-

References:

Change to alternative regimen before progression:


Treatment until progression


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

No further information

**References:**

**Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better**


**Limitations of palliative chemotherapy**


**Metaanalyses**

HRQOL is one of the key indicators of treatment benefit in advanced breast cancer, but contemporary systemic therapies in this setting do not appear to affect HRQOL differentially.
MBC HER2 negative Cytotoxic 1st-Line Therapy (10/20)

No further information

References:


Liposomal doxorubicin is equally effective to doxorubicin but has less cardio and myelotoxicity but more skin toxicity (O’Brien et al, 2004).
Polychemotherapy with anthracyclines and taxanes induce high remission rates but are more toxic then anthracycline or taxane free combinations.
After anthracycline treatment two studies could show a survival benefit with gemcitabine paclitaxel or with Docetaxel/Capecitabine (O’Shaugnessy et al, 2002 and Albain, 2004).
Retrospective date show that patients who respond to first line therapy with a complete response have a survival benefit compared to patients without CR (Greenberg et al, 1996).
Doxorubicin/docetaxel vs. Doxorubincin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL. Cassier et al., Breast Cancer Research and Treatment (electronic publication 2007).
Individual trials

NabPaclitaxel vs Ixabepilone vs paclitaxel +/- bevacizumab


Nab-Paclitaxel


Ixabepilone + capecitabine vs capecitabine alone


Metaanalyses

Docetaxel alone or in combination
Metaanalysis; MBC
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.


Cochrane analysis taxane-containing regimens for metastatic breast cancer

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

No further information

No references
MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (12/20)

Further information and references:

Consent: Eribulin: 5++, 21+, 4+/-


Suggested after anthracyclines (in alphabetical order): Capecitabine, Docetaxel, study-integrated experimental therapies, Gemcitabine, Pegliposomales Doxorubicin, Paclitaxel and Vinorelbine.

As monotherapy after anthracyclin-pretreatment only Docetaxel improved OAS as compared to a standard treatment arm in a prospective randomized trial in metastatic breast cancer (Nabholtz et al, 1999).

A Cochrane-metaanalysis of taxane treatment in metastatic 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 Pegliposomal Doxorubicin was superior to docetaxel alone in a randomised phase III trial by Sparano et al. It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantage from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.
Nab-paclitaxel


Metaanalysis

1. Cochrane analysis taxane-containing regimens for metastatic breast cancer
Further information:

Consent:

Capecitabine/Vinorelbine: ++: 16; +: 2; +/-: 0; -: 0; --: 0
Taxane/anthracycline re-challenge: ++: 1; +: 20; +/-: 6; -: 0; --: 0
Metronomic therapy: ++: 0; +: 13; +/-: 9; -: 0; --: 0

References:

Ixabepilone:


Gemcitabine/vinorelbine


Systematic review


Eribulin

Meta-analysis and evaluation

**Phase III trials**


**Taxane re-challenge**


**Anthracycline re challenge**


**Metronomic chemotherapy**


Gemcitabine + cisplatin / carboplatinum


Review

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (14/20)

Further information and references:

Consent:

Carboplatin (vs. Docetaxel): 2++, 11+, 19+/
Carboplatin in gBRCA mutation: 1++, 26+
Gemcitabine/Cisplatin (vs. GemPac): 1++, 18+, 10+/

Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:


Gemcitabine/Cisplatin (vs. GemPac)

Triple negative patients

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (15/20)

Further information and references:

Consent 2014:
Cap+Bev as maintenance after Doc+Bev: 1++, 3+, 22+-, 4-
2nd line as treatment through multiple lines: 19+-, 4-

Cap+Bev as maintenance after Doc+Bev:


2nd line as treatment through multiple lines:


**Individual trials**

**Taxanes +/- Bevacizumab**

NabPaclitaxel vs Ixabepilone vs paclitaxel

Review and opinion

“Despite setbacks, angiogenesis will likely remain an important target of treatment for selected patients with MBC.”

Side effects

Metaanalysis:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (16/20)

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab: ++: 12; +: 13; +/-: 0; -: 0; --: 0
Vinorelbine + trastuzumab – pertuzumab: ++: 0; +: 5; +/-: 17; -: 0; --: 0
Taxanes + lapatinib: ++: 1; +: 3; +/-: 9; -: 4; --: 0
Taxanes + trastuzumab + everolimus: ++: 0; +: 2; +/-: 9; -: 14; --: 0

References:


Docetaxel + trastuzumab + pertuzumab

**Pertuzumab side effects**


**Paclitaxel weekly + trastuzumab + pertuzumab**


**Vinorelbine + trastuzumab + pertuzumab**

1. Michael Andersson, José Manuel López-Vega, Thierry Petit, Claudio Zamagni, Margarita Donica, Julia Kamber, Edith A. Perez. The co-administration of pertuzumab (P) and trastuzumab (T) as a single infusion, followed by vinorelbine (V), in first-line (1L) treatment of HER2-positive locally advanced or metastatic breast cancer (MBC) patients (pts): VELVET study interim analysis. J Clin Oncol 33, 2015 (suppl; abstr 586)

**1st line chemotherapy + trastuzumab**

2. Valero V., Forbes J., Pegramet M. D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-
Gene-Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. DOI: 10.1200/JCO.2010.28.6450


6. Dang C et al., Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer, J Clin Oncol. 2015 Feb 10;33(5):442-7

**Trastuzumab mono**


**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 Jul;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) (17/20)

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab: ++: 12; +: 13; +/-: 0; -: 0; --: 0

References:

T-DM1


Capecitabine + lapatinib


When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.


Trastuzumab + lapatinib (if CT not possible)

Trastuzumab + lapatinib vs lapatinib


TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)

Review


Taxane + trastuzumab + pertuzumab
Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab
Trastuzumab mono
2nd line:


Trastuzumab + aromatase inhibitors (if ER+)


Lapatinib + aromatase inhibitors (if ER+)

Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2009.23.3734
Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (18/20)

Further information:

Consent:

Vinorelbine + lapatinib: ++: 0; +: 4; +/-: 21, -: 1; --: 0

References:

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel)


Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.


Capecitabine + lapatinib


Vinorelbine + lapatinib

**Trastuzumab + lapatinib (if CT not possible)**


**Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1)**

1. Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in

2. HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012


Lapatinib in HER2-positive Metastatic Breast Cancer (19/20)

No further information

References:

Anthracycline and Taxane and Trastuzumab pre-treatment


Trastuzumab naive patients: first line therapy


Brain metastases (radioresistance)

Immunodiagnostic Tests and Immunotherapy (20/20)

No further information

No references
Osteo-oncology and Bone Health
Osteocononology and Bone Health

- **Versions 2002-2015:**
  Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Hanf / Huober / Jackisch / Janni / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2016:**
  Fehm / Solomayer
Bisphosphonates in Metastatic Breast Cancer

- Hypercalcemia
- Reduction of skeletal events (complications)
- Reduction of bone pain
- Increasing bone pain-free survival
- Treatment beyond progression of bone met‘s

Oxford / AGO
LoE / GR

1a A ++
1a A ++
1a A ++
1a A ++
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 under bisphosphonates 4 C +/-
## Bone Modifying Agents for the Therapy of Bone Metastases

*for patients after zoledronate iv 4 mg q4w for 1 year or longer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate PO</td>
<td>1600 mg daily</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Clodronate IV</td>
<td>1500 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Pamidronate IV</td>
<td>90 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate IV</td>
<td>6 mg q3w / q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Ibandronate PO</td>
<td>50 mg daily</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Zoledronate IV</td>
<td>4 mg q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Zoledronate IV</td>
<td>4 mg q12w*</td>
<td>1a A +</td>
</tr>
<tr>
<td>Denosumab s.c.</td>
<td>120 mg q4w</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Denosumab s.c.</td>
<td>120 mg q12w</td>
<td>4 C -</td>
</tr>
<tr>
<td>Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis</td>
<td>5 D - -</td>
<td></td>
</tr>
</tbody>
</table>
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

- Marrow splints
- Plate osteosynthesis
- Compound osteosynthesis (replacement by PMMA and osteosynthesis)
- Vertebral replacement by titanspacer
- Tumor-Endoprosthesis
- Vertebroplasty / Kyphoplasty +/- thermoablation of the tumor
- Kypho-IORT (in studies only)*
- Resection of involved bone in oligometastatic disease (sternum, ribs, vertebrectomy and replacement with spondylodesis)

Oxford LoE: 3b  GR: C  AGO: +

*Study participation recommended
Metastatic Bone Disease: Radiotherapy (RT)

Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
  - Single dose RT = fractionated RT
- With neuropathic bone pain
- Asymptomatic isolated bone metastases
- Reduction of radiation induced pain flare by Dexamethasone

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th></th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td>With fracture risk</td>
<td>1a B ++</td>
</tr>
<tr>
<td>With functional impairment</td>
<td>1a B ++</td>
</tr>
<tr>
<td>With bone pain</td>
<td>1a B ++</td>
</tr>
<tr>
<td>Single dose RT = fractionated RT</td>
<td>2a B ++</td>
</tr>
<tr>
<td>With neuropathic bone pain</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Asymptomatic isolated bone metastases</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>Reduction of radiation induced pain flare by Dexamethasone</td>
<td>1b B +</td>
</tr>
</tbody>
</table>

Only few studies included breast cancer patients!
Recurrent bone pain in pre-irradiated parts of the skeleton

- Single dose RT*
- Fractionated RT*
- Radionuclid therapy
- Magnetic resonance-guided focused ultrasound
- Radiofrequency ablation
- Cryoablation

*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
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3% / 1.8%)
  - Association with (simultaneous) anti-angiogenic therapies
- Severe hypocalcemia (Dmab>BPs)
- Acute Phase Reaction* (IV Amino-BPs, Db) 10-30%
- Gastrointestinal side effects (oral BPs) 2-10%
- Atypical femur fractures
  - absolute risk of 11 per 10,000 person years of BP use

In adjuvant bisphosphonate therapy, major side effects were rarely observed (except APR*).
Recommendations for Precautions to Prevent ONJ*

- Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate or denosumab treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate or denosumab treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

- Good oral hygiene, limiting of alcohol intake and stopping smoking should be recommended

In adjuvant bisphosphonate therapy, ONJ was rare

*Osteonecrosis of the jaw
# Adjuvant Bone Targeted Therapy for Reduction of Bone Metastases and Survival Advantage

**Clodronate (oral)**
- Postmenopausal patients
- Premenopausal patients

**Aminobisphosphonates (iv or oral)**
- Postmenopausal patients
- Premenopausal patients

**Denosumab (60 mg s.c., q 6mo)**
- Postmenopausal patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clodronate (oral)</td>
<td>1a A +</td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td></td>
</tr>
<tr>
<td>Aminobisphosphonates (iv or oral)</td>
<td>1a A +</td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>Premenopausal patients</td>
<td></td>
</tr>
<tr>
<td>Denosumab (60 mg s.c., q 6mo)</td>
<td>1b^a B +/-</td>
</tr>
<tr>
<td>Postmenopausal patients</td>
<td></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 residronate (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 of Tumor Therapy-Induced Bone Loss / Osteoporosis</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 with 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>
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis

Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

- Physical activity 4 C ++
- Avoiding immobilisation 4 C ++
- Calcium (1000–1500 mg/d)** 4 C ++
- Vitamine D3 suppl. (800–2000 U/d) 4 C ++
- Cessation of smoking, reduction of alcohol 2b B ++
- Avoiding BMI < 20 mg/m² 3b C ++
- 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</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>**</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Alendronate 70 mg po/w*</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Denosumab 60 mg sc/6m*</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Ibandronate 150 mg po/m*</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Ibandronate 3 mg iv/3m</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84) 100 µg sc/d</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Raloxifene 60 mg po/d (improves spine only)</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Risedronate 35 mg po/w*</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Strontium ranelate 2 g po/d **</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Teriparatide (1-34) 20 µg sc/d</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Zoledronate 5 mg iv/12 m*</td>
<td>1b</td>
<td>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 -1,5</td>
</tr>
<tr>
<td>Frau 50-60</td>
<td>50-65 60-70</td>
</tr>
<tr>
<td>60-65</td>
<td>60-70 70-75</td>
</tr>
<tr>
<td>65-70</td>
<td>70-80 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-Score³⁺⁻⁴, wenn:
- Glukokortikoide oral ≥ 2,5 mg und < 7,5 mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis +0,5)
- Diabetes mellitus Typ 1
- ≥ 3 niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)
Osteo oncology and Bone Health (2/19)

No further information

No references
Bisphosphonates in Breast Cancer (3/19)

No further information

References:

Metaanalysen and Reviews (metastatic breast cancer):


Results of Phase III trials (metastatic breast cancer):

6. Rosen LS, Gordon DH, Dugan W et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004; 100:36-43
Denosumab in Metastatic Breast Cancer (4/19)

No further information

References:

Denosumab - Therapy of bone metastases and skeletal related complications:


Statement: Progression under bisphosphonates

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 (6/19)

No further information

References:

Reviews / Overview


<sup>186</sup>Rhenium (<sup>186</sup>Re-HEDP)


\[ {^{153}}\text{Samarium (}^{153}\text{Sm-EDTMP)} \]


\[ {^{89}}\text{Strontium (}^{89}\text{Sr-Chlorid)} \]


\[ {^{223}}\text{Ra-dichloride:} \]

Metastatic Bone Disease of the Spine – Indication for surgery (7/19)

Further information:

References:

**Bone Metastases Acute Spinal Cord Compression / Paraplegia (8/19)**

**Further information:**

**References:**


Surgery for Bone Metastases (9/19)

Further information:

References:

Metastatic Bone Disease: Radiotherapy (10/19)

Further information:

References:

Metastatic Bone Disease Recurrent Bone Pain (11/19)

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) (12/19)

Further information:

References

Bisphosphonates

Denosumab

Recommendations for Precautions to Prevent ONJ (13/19)

Further information

References:

Adjuvant Bisphosphonates for Reduction of Bone Metastases and Survival Advantage (14/19)

No further information

References:

Clodronate:


Adjuvant Aminobisphosphonates


**Dosage of Adjuvant Bisphosphonates for Improvement of Survival (15/19)**

*No further information*

**References:**

Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (16/19)

No further information

References:

2. German guidelines for the treatment of osteoporosis by the DVO:
Therapy and Prevention of Tumor Therapy-Induced Bone Loss / Osteoporosis (17/19)

No further information

References:

Medical Treatment of Osteoporosis (18/19)

No further information

References:

1. German guidelines for the treatment of osteoporosis by the DVO:

Raloxifen


Strontium renalate

Guidelines of the DVO (19/19)

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

- **Versions 2003–2015:**
  Bauerfeind / Bischoff / Böhme / Brunnert / Diel / Fehm / Friedrich / Friedrichs / Gerber / Hanf / Janni / Lück / Maass / Oberhoff / Rezai / Schaller / Seegenschmiedt / Solomayer / Souchon

- **Version 2016:**
  Lux / Schütz
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 of Metastases Surgery or Ablation

- Histological / cytological verification
  - Oxford / AGO LoE / GR: 3 B +
- Systemic treatment preferred
  - Oxford / AGO LoE / GR: 2a B ++*
- Consider surgery only in case of good response to palliative treatment
  - Oxford / AGO LoE / GR: 2b C +
- Metastases surgery is an option in good condition pts. with late onset oligometastases
  - Oxford / AGO LoE / GR: 3a B +
- Surgical treatment in the case of pain, exulceration, persistance after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression
  - Oxford / AGO LoE / GR: 5 D +/-
- Systemic treatment after surgery
  - Oxford / AGO LoE / GR: 5 D ++

* See chapters with systemic treatment recommendations
Local Therapy in Primary Metastatic Disease

- Local surgical treatment (R0) of primary tumor
  - Oxford / AGO
  - LoE / GR
  - 1b B +/-
- Axillary surgery for cN1
  - Oxford / AGO
  - LoE / GR
  - 5 C +/-
- Sentinel in cN0
  - Oxford / AGO
  - LoE / GR
  - 5 C -
- Local radiotherapy of primary tumor
  - Alone
    - Oxford / AGO
    - LoE / GR
    - 3a C +/-
  - After local surgical treatment with BCS or mastectomy and indication
    - Oxford / AGO
    - LoE / GR
    - 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, stereotactastic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT), radiochemoembolization, other modalities]

- Thermoablation
  - (RFA, LITT, cryotherapy)

Oxford / AGO LoE / GR

3a  B  +/-
3b  C  +/-
4   C  +/-
3b  C  +/-
Pulmonary Metastases
Local Therapy

- Before surgery: staging and biopsy (fine-needle aspiration with CT-guidance or transbronchial needle aspiration) 3a B +
- Resection of pulmonary metastases by VATS or conventional resection
  - In case of multilocular metastatic disease 3a B -
  - In case of single metastases on one side with curative intent 3a B +/-
- Thermoablation (CT-guided RFA, LITT) 3b C +/-
- Regional radiotherapy 4 C +/-
  - (e.g. stereotactic body radiosurgery with volumetric intensity modulated arc therapy (SRS-VMAT))
Malignant Pleural Effusions (MPE)

Incidence:
- ~ 10% of all breast cancer patients
- ~ 50% of patients with advanced breast cancer
- ~ 30% of all MPE are caused by breast cancer

Clinical presentation:
- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic [dyspnea (80%), dull chest pain (30%), nonproductive cough (10%)]
- Survival is related to the presence of additional metastases, age, ECOG PS and extent of involving the pleural surface

Diagnostic procedures:
- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion [cytology (→ 50% false negative), histology by thoracoscopy]
Malignant Pleural Effusion (MPE) Local Therapy

- 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)
- Continous pleural drainage
- Systemic treatment after pleurodesis
- Local antibody therapy (i.e. Catumaxomab )
- Serial thoracocentesis

* Adequate pain-relief
VATS: video-assisted thoracoscopic surgery
Malignant Ascites
Local Therapy

Ascites:
- Puncture, drainage in symptomatic patients 4 D ++
- Systemic therapy 3b D ++
- Local chemotherapy 3b D +/-
- Local antibody therapy (i.e. Catumaxomab) 3b D +/-
Malignant Pericardial Effusion
Local Therapy

Symptomatic pericardial effusion:

- Drainage, fenestration: 3b B ++
- VATS (video-assisted thorac. surgery): 4 D +
- US-guided puncture + instillation of mitoxantrone, cisplatin: 4 D +/-
Bone Marrow Involvement Associated with Pancytopenia

- **Weekly chemotherapy with***:
  - Epirubicin, Doxorubicin, Paclitaxel
  - Capecitabine

- **HER2 pos.: add anti-HER2 treatment**

* Consider pre-treatment

---

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>D</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin, Doxorubicin, Paclitaxel</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>HER2 pos.: add anti-HER2 treatment</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>
Soft Tissue Metastasis
Local Therapy

Surgery in locoregional limited metastatic disease (skin, muscular, nodal) in case of complete resection (R0) and no further metastases after staging

Radiotherapy (if no immediate surgery is indicated or even after surgery):

- Paresis, spinal cord compression
- Plexus infiltration
- Soft tissue metastasis

Oxford / AGO
LoE / GR

4 C +

2b C ++

3b C ++

3b C +
Specific Sites of Metastases (2/13)

No further information

No references
Specific Sites Of Metastases (3/13)

No further information

No references
General Aspects of Metastases Surgery or Ablation (4/13)

No further information

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 +/-)

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 +)

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
Liver Metastasis - Local Therapy (6/13)

Further information and references:

Vote result of the AGO recommendation (complete slide without further changes): yes = 23/ no = 2

Statements:
Resection of liver metastasis (R0) (3a B+/−)
HR positive: chemotherapy sensible, long disease-free interval, absence of extrahepatic disease, ≤ 3 metastases
Her2 positive: age < 50 y., metastasis < 5 cm, no further metastases


**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,
   Apr;189(2):151-5.
   May;110(18):313-8.
4. Zamboni MM, da Silva CT Jr, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in
5. Li Z, Pantanowitz L, Khalbuss WE, Arya P, Monaco SE. Challenges in diagnosing metastatic breast carcinoma in
Malignant Pleural Effusion - Local Therapy (9/13)

Further information and references:

Vote result of the AGO recommendation (complete slide without further changes): yes = 19/ no = 1

Statement: If expected survival is short, less invasive procedures should be considered (4 C ++)


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: Continuous pleural drainage (2a B+)


Statement: Systemic treatment after pleurodesis (3b C+/-)

Statement: Local antibody therapy (i.e. Catumaxomab) (3b C -)

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:

**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 2003–2015:** Bischoff / Diel / Friedrich / Gerber / Huober / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

- **Version 2016:** Loibl / Müller

In collaboration with:

P. Feyer und D. Rades (DEGRO)
CNS Metastases in Breast Cancer – Incidence

- Breast cancer is the 2\textsuperscript{nd} most common cause of CNS metastases

- At autopsy:
  - Parenchymal CNS metastases: \(\sim30–40\%\)
  - Leptomeningeal CNS metastases: \(\sim5–16\%\)

- Increasing incidence (10 \(\Rightarrow\) 40 \%)

- Increasing incidence due to
  - More effective treatment of extracerebral sites with improved prognosis
  - Increasing use of MRI in diagnostic evaluation

- Lack of specific knowledge about treatment of brain metastases in breast cancer since most studies are not breast cancer specific. Therefore, participation in the German registry study is recommended (www.gbg.de)
CNS Metastases in Breast Cancer (BC) Risk Factors

- **Primary Tumor:**
  - Negative estrogen receptor status (basal-like cell type / triple negative)
  - High grading, high Ki-67 index
  - HER2 and/or EGFR (HER1) overexpression

Brain metastases are more likely to be estrogen receptor negative and overexpress HER2 and/or EGFR

There is no evidence for BM-screening in asymptomatic BC-patients
Graded Prognostic Assessment (GPA)
Worksheet to Estimate Survival from Brain Metastases (BM) by Diagnosis

<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>
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<tbody>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
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<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
<td>LumA</td>
<td>HER2</td>
<td>LumB</td>
<td>_____</td>
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<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>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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
Background OS-Score (Rades et al.)

- Based on a multivariate analysis of 1,085 patients treated with WBRT alone for brain metastases, a scoring system was developed.
- This score was based on the four independent prognostic factors that were significantly associated with survival on multivariate analysis: age, performance status, extracranial metastases at the time of WBRT, and interval between tumor diagnosis and WBRT.
- The score for each prognostic factor was determined by dividing the 6-month survival rate (in %) by 10.
- The total score for each patient represented the sum of the scores for each prognostic factor.
- Total scores ranged from 9 to 18 points, and patients were divided into four groups.
**WBRT: Survival Score (N=1,085)**

| Score is already validated (350 new patients). |

<table>
<thead>
<tr>
<th>Überleben nach 6 Monaten (%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alter</td>
<td></td>
</tr>
<tr>
<td>≤ 60 Jahre</td>
<td>43</td>
</tr>
<tr>
<td>≥ 61 Jahre</td>
<td>25</td>
</tr>
<tr>
<td>Karnofsky-Index</td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>8</td>
</tr>
<tr>
<td>≥ 70</td>
<td>53</td>
</tr>
<tr>
<td>Extrakranielle Metastasen</td>
<td></td>
</tr>
<tr>
<td>Nein</td>
<td>51</td>
</tr>
<tr>
<td>Ja</td>
<td>24</td>
</tr>
<tr>
<td>Intervall von Erstdiagnose bis GHRT</td>
<td></td>
</tr>
<tr>
<td>≤ 8 Monate</td>
<td>32</td>
</tr>
<tr>
<td>&gt; 8 Monate</td>
<td>36</td>
</tr>
</tbody>
</table>

- **Rades et al., STO 2008**
- **Dziggel et al., STO 2013**
Single / Sole Brain Metastases

Local therapy alone: SRS (≤4cm) o. FSRT o. Resection
WBRT + Boost (SRS, FSRT) o. Resection + WBRT
Resection + Irradiation of the tumor bed (without WBRT)
WBRT alone*

- WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.
- WBRT impaires neurocognitive function.
- In case of resection of the tumor the tumorbed has to be irradiated (either local RT or boost in case of WBRT).
- In general there is no advantage of surgical resection over RT.

* Patients with reduced general conditions and limited life expectancy

SRS = stereotactic radiosurgery (single session)  
FSRT = fractionated stereotactic RT  
WBRT = whole brain radiotherapy
2-3 (2-4) Brain Metastases (Oligo-)

Local therapy alone: SRS (≤ 4 cm) or FSRT

WBRT + Boost (SRS, FSRT)

WBRT alone *

- WBRT in addition to SRS/FSRT or tumor resection does improve local control and symptoms, but without prolongation of overall survival.
- *WBRT impaires neurocognitive function.

* Patients with reduced general conditions and limited life expectancy

SRS = stereotactic radiosurgery (single session)
FSRT = fractionated stereotactic RT
WBRT = whole brain radiotherapy

Oxford/AGO
LoE / GR
2b B ++
2a B ++
2b B +
NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy (WBRT) in Addition to Radiosurgery (SRS) in Patients with 1 to 3 Brain Metastases

Study design:

Patients with 1-3 brain metastases, each < 3 cm by contrast MRI, were randomized to SRS alone or SRS + WBRT and underwent cognitive testing before and after treatment. The primary endpoint was cognitive progression (CP) defined as decline > 1 SD from baseline in any of the 6 cognitive tests at 3 months. Time to CP was estimated using cumulative incidence adjusting for survival as a competing risk.

Conclusion:

Decline in cognitive function, specifically immediate recall, memory and verbal fluency, was more frequent with the addition of WBRT to SRS. Adjuvant WBRT did not improve OS despite better brain control. Initial treatment with SRS and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases that are amenable to SRS.

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

| 2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation |
|--------------------------------------------------|------------------|------------------|
| after surgical resection (n=160)                    | after radiosurgery (n=199) |
| WBRT     | observation | WBRT     | observation |
| Local recurrence       | 27% | 59% (p<0.001) | 19% | 31% (p=0.040) |
| New lesions           | 23% | 42% (p=0.008) | 33% | 48% (p=0.023) |

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

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:

• No need for rapid decompression
• No need for histological verification
• Tumor location poorly amenable to surgery
• More than two lesions
## Multiple Brain Metastases >3 (4) Lesions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT (supportive steroids*)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Hippocampus-sparing radiotherapy</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Radiochemotherapy for cerebral disease control</td>
<td>3b C -</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>3a D +/-</td>
</tr>
<tr>
<td>Corticosteroids alone*</td>
<td>3a B +/-</td>
</tr>
</tbody>
</table>

*Adapted to symptoms
Systemic and Symptomatic Therapy of Brain Metastases

- Continue anti-HER2-treatment
  - Oxford / AGO LoE / GR
    - 2c C +

- Lapatinib + Capecitabine as initial treatment
  - (HER2 pos. disease)
  - Oxford / AGO LoE / GR
    - 1b B +/-

- Chemotherapy alone as primary treatment
  - Oxford / AGO LoE / GR
    - 3 D -

- Anticonvulsants only if symptoms of seizures
  - Oxford / AGO LoE / GR
    - 3 C +

- Glucocorticoids only when symptoms and / or mass effect
  - Oxford / AGO LoE / GR
    - 3 C ++
Leptomeningeal Carcinomatosis

Local Therapy

**Intrathecal or ventricular therapy**

- MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)
- Liposomal cytarabine 50 mg, q 2w
- Thiothepa
- Steroids
- Trastuzumab (HER2 pos. disease)

**Radiotherapy**

- Focal (bulky disease)
- WBRT
- Neuroaxis (disseminated spinal lesions)

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX 10–15 mg 2–3x/ week (+/- folinic acid rescue)</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Liposomal cytarabine 50 mg, q 2w</td>
<td>3b</td>
<td>C</td>
</tr>
<tr>
<td>Thiothepa</td>
<td>3b</td>
<td>C</td>
</tr>
<tr>
<td>Steroids</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Trastuzumab (HER2 pos. disease)</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Focal (bulky disease)</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>WBRT</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>Neuroaxis (disseminated spinal lesions)</td>
<td>4</td>
<td>D</td>
</tr>
</tbody>
</table>

Due to bad prognosis consider best supportive care, especially in patients with poor performance status.
CNS Metastases in Breast Cancer (2/15)

No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/15)

No further information

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):


References 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 (5/15)

No further information

References:

References for Breast-GPA:

Further References: Prognostic Factors for Survival:


**Rades OS-Score (6-7/15)**

*No further information*

**Reference:**

Singe / Solitary Brain Metastases (8/15)

No further information

References:


Brain Metastases 2-3 (2-4) lesions (9/15)

No further information

References:

See references Slide 8
NCCTG N0574 (Alliance): (10/15)

No further information

Reference:

EORTC 22952-26001 Study (11/15)

No further information

Reference:

Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (12/15)

No further information

No references
**Multiple Brain Metastases (13/15)**

No further information

**References:**

Radiochemotherapy


Systemic and Symptomatic Therapy of Brain Metastases (14/15)

No further information

References:


Chemotherapy

Anticonvulsants


Steroids

Leptomeningeal Carcinomatosis Local Therapy (15/15)

No further information

References:


**Trastuzumab intrathecal**


MTX high dose

Complementary Therapy
Survivorship
Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

Versions 2002–2015:
Albert / Bauerfeind / Blohmer / Fersis / Friedrich / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

Version 2016:
Kümmel / Schmidt
„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
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

Preoperative:

- Hypnosis (reduces anxiety, pain, fatigue, nausea) 1b B +

Postoperative:

- Acupuncture (pain relief, anxiety, muscular discomfort) 2b B +/-
- Acupuncture (nausea, vomiting) 2b B +
- Massage Therapy (pain relief) 2b C +/-
- Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage) 1a A +
- Prophylactic lymph drainage 1b B -
### Complementary Treatment

**Impact on Toxicity I**

<table>
<thead>
<tr>
<th>Complementary Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>While on anti-cancer treatment: beware of drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Mistletoe (Viscum album)</strong> in order to reduce side effects</td>
<td>1a B +/-</td>
<td></td>
</tr>
<tr>
<td>(influence on efficacy of anti-tumor therapy unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Thymic peptides</strong> (lowered risk of severe infections)</td>
<td>2a B +/-</td>
<td></td>
</tr>
<tr>
<td>(influence on efficacy of anti-tumor therapy unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Ginseng</strong> (in order to reduce cancer related fatigue)</td>
<td>2b C -</td>
<td></td>
</tr>
<tr>
<td>(note: ginseng inhibits cytochrome P enzymes e.g. CYP 3A4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Ganoderma Lucidum</strong> (may improve fatigue, note: inhibits cytochrome P enzymes e.g. CYP 3A4)</td>
<td>2b C -</td>
<td></td>
</tr>
<tr>
<td>➢ <strong>L-Carnitine</strong> (given for prevention of toxicity, increased chemotherapy induced peripheral neuropathy)</td>
<td>1b B --</td>
<td></td>
</tr>
<tr>
<td>➢ <strong>L-Carnitine does not improve cancer rel. Fatigue</strong></td>
<td>1b B --</td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Curcumin as an adjunct to reduce radio dermatitis</strong></td>
<td>1b B +/-</td>
<td></td>
</tr>
<tr>
<td>➢ <strong>Ginger for chemotherapy induced nausea &amp; vomiting</strong></td>
<td>1b C +/-</td>
<td></td>
</tr>
<tr>
<td>(consider interaction with anti-tumor drugs)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

While on anti-cancer treatment: beware of drug interactions.
### Complementary Treatment Impact on Toxicity II

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / LoE</th>
<th>AGO GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant supplements</td>
<td>1b B</td>
<td>-</td>
</tr>
<tr>
<td>High dose vitamine C</td>
<td>1b C</td>
<td>-</td>
</tr>
<tr>
<td>Vitamine E</td>
<td>2b D</td>
<td>-</td>
</tr>
<tr>
<td>Selenium for alleviating side effects of therapy</td>
<td>1b B</td>
<td>-</td>
</tr>
<tr>
<td>Co-Enzyme Q 10 (fatigue, QoL)</td>
<td>1b B</td>
<td>-</td>
</tr>
<tr>
<td>Proteolytic enzymes in order to reduce chemotherapy-induced toxicity</td>
<td>3b B</td>
<td>-</td>
</tr>
<tr>
<td>Chinese herbal medicine improves wound healing after mastectomy</td>
<td>1b B</td>
<td>-*inf</td>
</tr>
<tr>
<td>Oxygen and ozone therapy</td>
<td>5 D</td>
<td>- -</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
  - May offer some benefit to breast cancer patients in terms of bone marrow improvement and quality of life

- Homoeopathic medicines for adverse effects of cancer treatments
  - 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)
  - Treatment of chemotherapy induced polyneuropathy

Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of Evidence</th>
<th>Grade</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Chinese medicinal herbs</td>
<td>1b B</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Homoeopathic medicines</td>
<td>1b B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Topical Silymarin</td>
<td>3a B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1a B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>5 D</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1a B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1a B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Leucopenia (Moxibustion)</td>
<td>2b B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Treatment of chemotherapy induced polyneuropathy</td>
<td>2ba B</td>
<td>-</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
**Complementary Treatment**

**Mind-Body Medicine II**

- **Yoga**
  - Improves sleep, quality of life, stress, anxiety, depression
  - Improves 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

---

**Oxford / AGO**

**LoE / GR**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Score 1b</th>
<th>Score 2a</th>
<th>Score A</th>
<th>Score +/−</th>
</tr>
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<tbody>
<tr>
<td>Yoga</td>
<td>1b</td>
<td></td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Qi Gong</td>
<td></td>
<td></td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Tai Chi</td>
<td>1b</td>
<td></td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Hypnosis (in combination with cognitive training)</td>
<td></td>
<td></td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Modifiable Lifestyle Factors
Prevention of Recurrence I

- **Physical exercise**
  (Equivalents to 3–5 hrs moderate walking per week improves DFS and OS, cardio-respiratory fitness, physical functioning)

- **Smoking**

- **Alcohol consumption (≥6 g/day)**
Modifiable Lifestyle Factors

Nutrition after Breast Cancer Diagnosis
Prevention of Recurrence II

- Adherence to normal BMI/weight loss if overweight, irrespective of HR-status (improves prognosis – DFS/OS)
  
- Low fat diet (improves prognosis – DFS and OS)
- Dietary counseling recommended

- Avoid high-fat dairy products

- Flaxseed/increased fibre intake

- Adherence to general nutrition guidelines (e.g. DGE, WCRF)

- Dietary extremes (are associated with less favourable outcomes)

Oxford /AGO
LoE / GR

1a  A  ++
1a  A  +
2b  C  +
2a  B  +
2a  B  ++
1b  B  --
Complementary Treatment
Prevention of Recurrence III
Dietary Supplements – Herbal Therapies

Post treatment vitamin/antioxidant supplements don'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**
  - Vitamine supplementation in pats on a balanced diet (esp. Vit C, E, D)
    - Artificial carotenoids appear to be associated with worse outcome
  - **Proteolytic enzymes**
  - Soy-food (natural source of phytoestrogenes)
  - Black Cohosh (Cimicifuga racemosa)
  - Mistletoe (Viscum album)
  - Thymic peptides (impact on OS)
  - Oxygen- and ozone therapy
  - Antioxidant supplements (after completion of radiotherapy)
  - Laetrile
  - Cancer bush (Sutherlandia frutescens), Devil's claw (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis), Bambara groundnut (Vignea subterranean)

<table>
<thead>
<tr>
<th>Oxford</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B +/-</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>2a</td>
<td>B +/-</td>
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<tr>
<td>2b</td>
<td>B -</td>
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<tr>
<td>3b</td>
<td>B -</td>
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<tr>
<td>2a</td>
<td>B +/-</td>
</tr>
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<td>B -</td>
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<td>B +/-</td>
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<td>B -</td>
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<td>2b</td>
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<td>1c</td>
<td>D -</td>
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<tr>
<td>5</td>
<td>D - -</td>
</tr>
<tr>
<td>5</td>
<td>D - -</td>
</tr>
</tbody>
</table>

For Further Information and References see www.ago-online.de
Complementary Treatment
Cancer Pain Reduction

- Acupuncture for cancer pain in adults
  1a B +/-

- Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults
  2b D +/-

- Cave: No delay in diagnostic process
Further information:

Screened Data Sources:
Pubmed  2003 - 01/2016
ASCO  2003 – 2015
SABCS  2003 – 2015
EBCC  2003 – 2015
Cochrane library: summary Jan. 2016:

External advice:

The commission wants to thank the following external advisors for their contribution:

2010:  Advice on nutritional facts by Prof. Dr. G. Stangl, Martin-Luther-University Halle Wittenberg, Germany
2011, 2013, 2015, 2016: Prof. Dr. G. Dobos and team,
    Alfried Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen,
    Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references
Further information:

The term „alternative therapies“ has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.
- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

No References
General Considerations (4/14)

No further information

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:

Mistletoe:


**Thymus:**


**Ginseng, Ganoderma lucidum:**


L-Carnitine:


Curcumin:

Complementary Treatment. Treatment phase. Impact on Toxicity II (7/14)

No further information

References:

Antioxidant supplements


Vitamin C


Selen


Coenzyme 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


References:

Yoga

Qigong


Tai Chi


Tai Chi Abstimmungsergebnis der AGO-Empfehlung: 10/7

Hypnosis


Modifiable Lifestyle Factors – Nutrition after Breast Cancer Diagnosis – Prevention of Recurrence I (11/14)

No further information

References:

Physical exercise

Improvements in DFS and OS, prevention of recurrence


Smoking


Alcohol

diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment.


Modifiable Lifestyle Factors – Nutrition after Breast Cancer Diagnosis – Prevention of Recurrence 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 III (13/14)

No further information

References:

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
Hormone (Replacement) Therapy (HT) of Estrogen Deficiency after Diagnosis of Breast Cancer

- **Endocrine responsive disease**
  (HT may increase risk)
- **Endocrine non-responsive disease**
  (apparently no risk increase)
- **Endocrine responsive disease**: combined treatment TAM plus low-dose-HT
- **Tibolone**
- **Topical vaginal application of**
  - Estriol (E3 0.03 mg)
  - Estradiol (E2) during AI therapy

**Oxford / AGO**

<table>
<thead>
<tr>
<th>Endocrine responsive disease</th>
<th>Endocrine non-responsive disease</th>
<th>Endocrine responsive disease: combined treatment TAM plus low-dose-HT</th>
<th>Tibolone</th>
<th>Topical vaginal application of</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b B -</td>
<td>2a B +/-</td>
<td>2b B +/-</td>
<td>1b A - -</td>
<td>4 D +/-</td>
</tr>
<tr>
<td>4 C -</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

LoE / GR
## Alternative 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
  - 1st choice: venlafaxine
  - 2nd choice: desvenlafaxine
  - 3rd choice: sertraline, escitalopram
- **Gabapentin** (BC and TAM-use)
- **Pregabalin**
- **Clonidin** (BC and TAM-use)
- **MPA (i.m. 500 mg single shot)**
  (most potent, but endocrine agent!)
- **Vitamine E**
- **Melatonin** (improvement in sleep quality)
While anti-cancer treatment: Beware of drug interactions!

<table>
<thead>
<tr>
<th>CAM - Approaches to Reduce Menopausal Symptoms II</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-derived phytoestrogens – isoflavonoids</td>
<td>1b B -</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Topical vaginal application</td>
<td></td>
</tr>
<tr>
<td>Red Clover isoflavonoids</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Hot flush, sleep disturbance</td>
<td></td>
</tr>
<tr>
<td>(might stimulate BC especially in endocrine responsive disease)</td>
<td></td>
</tr>
<tr>
<td>Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d)</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>(reduces relapses no effect on hot flashes)</td>
<td></td>
</tr>
<tr>
<td>Black Cohosh for hot flushes</td>
<td>1b B -</td>
</tr>
<tr>
<td>Black cohosh + St.John´s Worth</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>St. John´s Wort (in combination-therap)y</td>
<td>1b B --</td>
</tr>
<tr>
<td>(pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)</td>
<td></td>
</tr>
<tr>
<td>Ginseng root (Panax ginseng or P. quinquefolius)</td>
<td>1b B -</td>
</tr>
<tr>
<td>Bromelain + Papain + Selen + Lektin (for, AI induced joint symptoms)</td>
<td>3b B +</td>
</tr>
</tbody>
</table>
General Approaches to Reduce Menopausal Symptoms III

General approaches:

- Physical exercise 1b B ++
- Mind body-medicine (yoga, hypnosis, education, counselling) 1b B +
- Cognitive behavioral therapy (CBT) 1b B ++
- Acupuncture
  - Aromatase-inhibitor treatment induced arthralgia 2b B +
  - Hot flashes 1b B +
  - Depression 2b B +/-
  - Anxiety, Sleep 3b C +/-

(no acupuncture in tumor bearing region, possibility of cell seeding)
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

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

Impairment of CT – effect cannot be excluded!

- Fertility preservation counselling
- Fertility preservation with assisted reproduction therapy
  (further information www.fertiprotect.de)
# 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>
</tr>
<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 chemotherapy</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>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Badaway (2009)</td>
<td>0.06</td>
<td>0.02-0.20</td>
<td>4/39</td>
<td>26/39</td>
</tr>
<tr>
<td>Sverrisdottir 1 (2009)</td>
<td>0.19</td>
<td>0.04-1.06</td>
<td>14/22</td>
<td>18/20</td>
</tr>
<tr>
<td>Sverrisdottr 2 (2009)</td>
<td>2.03</td>
<td>0.31-13.27</td>
<td>27/29</td>
<td>20/23</td>
</tr>
<tr>
<td>Del Mastro (2011)</td>
<td>0.27</td>
<td>0.14-0.54</td>
<td>13/148</td>
<td>35/133</td>
</tr>
<tr>
<td>Gerber (2011)</td>
<td>0.56</td>
<td>0.19-1.62</td>
<td>9/30</td>
<td>13/30</td>
</tr>
<tr>
<td>Sun (2011)</td>
<td>0.38</td>
<td>0.06-2.30</td>
<td>3/11</td>
<td>5/10</td>
</tr>
<tr>
<td>Munster (2012)</td>
<td>1.09</td>
<td>0.22-5.52</td>
<td>4/26</td>
<td>3/21</td>
</tr>
<tr>
<td>Elgindy 1 (2013)</td>
<td>0.76</td>
<td>0.18-3.25</td>
<td>4/25</td>
<td>5/25</td>
</tr>
<tr>
<td>Elgindy 2 (2013)</td>
<td>1.0</td>
<td>0.25-4.00</td>
<td>5/25</td>
<td>5/25</td>
</tr>
<tr>
<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><strong>Summary: Fixed effect</strong></td>
<td><strong>0.34</strong></td>
<td><strong>0.25-0.46</strong></td>
<td><strong>114/616</strong></td>
<td><strong>206/615</strong></td>
</tr>
<tr>
<td><strong>Summary: Random effect</strong></td>
<td><strong>0.36</strong></td>
<td><strong>0.23-0.57</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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) plus estradiol | • Serum level on cycle day 2–3  
• Variation between cycles possible  
• High FSH value is associated with poor response to ovarian stimulation |
| Anti Müllerian Hormone (AMH)              | • No specific timing for the test  
• Stable value within and between menstrual cycles  
• Low AMH value is associated with poor response to ovarian stimulation |
| Antral follicle count (AFC)               | • Number of visible follicles (2–10 mm) during transvaginal ultrasound  
• Performed on cycle days 2–5  
• Number of antral follicles correlates with ovarian response to stimulation |

All the tests do not predict failure to conceive, but they allow to counsel that the window of opportunity to conceive may be shorter than anticipated.
## Contraceptive Options for Women after Diagnosis of Breast Cancer

### Methods and Grades

- **Barrier methods**
  - 5 D +
- **Sterilization (tubal ligation / vasectomy)**
  - 5 D +
- **Non-hormonal intrauterine devices (IUDs)**
  - 3b D +
- **Levonorgestrel-releasing IUDs**
  - 2b C -
  - Removal in newly diagnosed patients
  - 4 D +/-
- **Timing methods**
  - 5 D -
- **Injectable progestin-only contraceptives**
  - 5 D -
- **Progestin-only oral contraceptives**
  - 5 D -
- **Combined oral contraceptives**
  - 5 D -
Emergency Contraception after Diagnosis of Breast Cancer

- Copper intrauterine device (Cu-IUD) 5 D +
- Levonorgestrel, Ulipristal 5 D +

Oxford / AGO LoE / GR
### Sexual Health

<table>
<thead>
<tr>
<th>Topic</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of factors to sexual dysfunction</td>
<td>5</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Use of patient-reported questionnaires</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Vaginal dryness: Non-hormonal lubricans / moisturizers</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Psychoeducational support, group therapy, sexual counseling, marital counseling, psychotherapy</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>
Assessment of Sexual Health

- Sexual Complaints Screener (SCS) for women*
  German Translation

Screening-Check-Fragebogen: Overall Sexual Function
1. Are you satisfied with your sexual function?
   yes, no; if no
2. How long have you been dissatisfied with your sexual function?
3. The problem(s) with your sexual function is: (mark one or more):
   1. Problem with little or no interest in sex
   2. Problem with decreased genital sensation (feeling)
   3. Problem with decreased vaginal lubrication (dryness)
   4. Problem reaching orgasm
   5. Problem with pain during sex
   6. Other
4. Which problem is most bothersome? (circle) 1, 2, 3, 4, 5, 6.
5. Would you like to talk about it with your doctor?

* Hatzichristou D, Rosen RC, Denogatis LR, Low WY, Sadovsky R, Symonds T.
Gynecological Issues in Breast Cancer Patients (2/15)

Further information:

Screened data bases:
- Pubmed 2009 –2015
- ASCO 2009 - 2015
- Cochrane 2009 - 2015
- Medline 2009 - 2015

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies

No references
Hormonal (Replacement) Therapy of Estrogen Deficiency after Diagnosis of Breast Cancer (3/15)

No further information

References:

- Endocrine responsive disease
  (HT may increase risk)
- Endocrine non-responsive disease
  (apparently no risk increase)
- Endocrine responsive disease: combined treatment TAM plus low-dose-HT


- 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 (Portman DJ, 2014). For urogenital problems vaginal moisturizers, isoflavone or topical estrogens can be used (Ghazanfarpour M, 2015; Loibl S, 2011).


Further information:

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. In breast cancer patients treated with tamoxifen and menopausal symptoms the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin is considered effective in treating hot flashes. (Haques R, 2015) The use of paroxetine and fluoxetine should be avoided because they may reduce the efficacy of tamoxifen. Increased breast cancer mortality is associated with the use of paroxetine and tamoxifen (Chubak J, 2016; Kelly 20 CM, 2010). Patients not being treated with tamoxifen the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes. Breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes. (Bordeleau L, 2010)

Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes. (L'Espérance S, 2013; Kontos M, 2010)

References:


SSRI:

Venlafaxine


**Desvenlafaxine**


**Paroxetine**


**Fluoxetine**


**Citalopram**


**Gabapentin**


**Pregabalin**


**Clonidin**


(D) MPA (depo-) (Medroxyprogesterone acetate)


**Vitamin 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. (Roberts H, 2010) A recent systematic review retrieved 8 RCTs involving 798 breast cancer patients. Traditional herbal medicine combined with conventional therapy in the treatment of breast cancer has been efficacious in improving QOL and in decreasing the number of hot flashes per day (Kim W, 2015). Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating. (Ma H, 2011)


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 gel (Ghazanfarpour M,, 2015).

**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 (Ghazanfarpour M, 2015).


**Flaxseed** has no effect on reducing hot flashes based on randomized phase III trial where it failed to demonstrate a significant reduction of hot flushes for postmenopausal patients taking additional 410 g of lignans as compared to placebo (Pruthi S, 2012).


Taken together neither **Black cohosh** (Cimicifuga racemosa) (Leach MJ, 2012) nor **St John’s Wort** (Caraci F, 2011) nor **Ginseng root** (Kim MS. 2013) showed a benefit regarding improvement of menopausal symptoms.


In a Phase III trial the fixed combination of Red Clover and St. Johns Wort were significantly better in reducing menopausal symptoms than placebo.

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. (Uhlenbrock B, 2010) But there were no reduction in other menopausal symptoms.

Further information:

Physical exercises (PE) and cognitive behavior therapy (CBT; this is one form of psychotherapy) have positive effects on menopausal symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. (Duijts SF, 2012; Pachman DR, 2010; Mann E, 2012). The CBT and PE are cost-effective. Prescription is recommended by the authors (Mewes JC, 2015).

Mind-Body-Medicine (MBM; Relaxation training, Yoga, Hypnosis) resulted in a moderate up to a significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. (Buffart LM, 2012; Cramer H, 2014). However these effects are seen even after a longer period of application and avoid after some months stopping MBM. Acupuncture can also be used but the results from RCT are conflicting. A meta-analysis showed significant effects of acupuncture compared with sham acupuncture, but marked heterogeneity was observed in this model. (Lee MS, 2009)

References:

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/15)

Further information:

Chemotherapy carries a risk of permanent ovarian failure. Ovarian protection is therefore discussed in patients who want to preserve fertility.

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

References:

Ovarian function protection CT+GNRH


during chemotherapy to reduce ovarian failure in early stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). J Clin Oncol 2014; ASCO abstract


**Fertility preservation counselling**


Fertility Preservation


Randomised Controlled Trials and Metaanalysis


Ovarian Function Preservation Comparison of Randomized Trials (8/15)

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 (9/15)

Further information

A recent meta-analysis of 12 randomized controlled trials investigated whether the use of LHRHa during chemotherapy in premenopausal breast cancer patients reduces treatment-related 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 \(I^2 = 47.1\\%\), P heterogeneity = 0.026). In eight studies reporting amenorrhea rates 1 year after chemotherapy completion, the addition of LHRHa reduced the risk of POF (OR 0.55, 95% CI 0.41–0.73, P < 0.001) without heterogeneity \(I^2 = 0.0\%\), P heterogeneity = 0.936). In five studies reporting pregnancies, more patients treated with LHRHa achieved pregnancy (33 versus 19 women; OR 1.83, 95% CI 1.02–3.28, P = 0.041; \(I^2 = 0.0\%\), P heterogeneity = 0.629). In three studies reporting DFS, no difference was observed (HR 1.00, 95% CI 0.49–2.04, P = 0.939; \(I^2 = 68.0\%\), P heterogeneity = 0.044)“ The authors concluded: „Temporary ovarian suppression with LHRHa in young breast cancer patients is associated with a reduced risk of chemotherapy-induced premature ovarian failure and seems to increase the pregnancy rate, without an apparent negative consequence on prognosis.“ (Lampartini M et al. 2015)

Reference:

Further information:

The menstruation history is reliable only in women < 45 years of age. A more precise evaluation, especially in perimenopausal patients is possible with the measurement of FSH and E2 levels in peripheral blood. Hormonal replacement should be stopped at least 6 weeks before measurement. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression [1,2]. Low AMH (antimuellerian hormone) levels seem to be indicative for reduced ovarian reserve and chemotherapy-related amenorrhea (CRA) in chemotherapy-treated breast cancer patients [3, 4,5,6].

Antral follicle count, defined as the sum of follicle diameters of all follicles of 10mm in both ovaries. [7]

References:

amenorrhea among premenopausal women with early stage breast cancer. Cancer Invest. 2008 Apr-May;26(3):286-95


Assessment of Ovarian Reserve (11/15)

No further information

Reference:

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 (12/15)**

No further information

**References:**

Emergency Contraception after diagnosis of breast cancer (13/15)

No further information

References:

Sexual Health (14/15)

No further information

References:

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Assessment of Sexual Health (15/15)

Further information:

Sexual Complaints Screener (SCS) for women
German Translation

References: