Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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

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2) Breast Cancer Risk and Prevention
3) Early Detection and Diagnosis
4) Pathology
5) Prognostic and Predictive Factors
6) Lesions of Uncertain Malignant Potential (B3) – ADH, LIN, FEA, Papilloma, Radial Scar
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8) Breast Cancer Surgery Oncological Aspects
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21) Osteooncology and Bone Health
22) Specific Sites of Metastases
23) CNS Metastases in Breast Cancer
24) Complementary Therapy & Survivorship
25) Gynecological Issues in Breast Cancer Patients
## Oxford Levels of Evidence (LOE)

<table>
<thead>
<tr>
<th>LOE</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
</tr>
</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 ≥ 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>
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<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; Research; Ecological studies</td>
<td>&quot;Outcomes&quot; Research</td>
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<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>
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<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 or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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### AGO Grades of Recommendation

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>++</strong></td>
<td>This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.</td>
</tr>
<tr>
<td><strong>+</strong></td>
<td>This investigation or therapeutic intervention is of limited benefit for patients and can be performed.</td>
</tr>
<tr>
<td>+/-</td>
<td>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.</td>
</tr>
<tr>
<td>-</td>
<td>This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.</td>
</tr>
<tr>
<td>--</td>
<td>This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.</td>
</tr>
</tbody>
</table>
### Abbreviations – I

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>10+ LN</td>
<td>≥ 10 tumor infiltrated axillary lymph nodes</td>
</tr>
<tr>
<td>A</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>ABCSG-8</td>
<td>Austrian Breast- and Colorectal Cancer Study Group</td>
</tr>
<tr>
<td>AC</td>
<td>Doxorubicin / cyclophosphamide</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Radiology</td>
</tr>
<tr>
<td>AD</td>
<td>Doxorubicin / docetaxel</td>
</tr>
<tr>
<td>ADH</td>
<td>Atypical ductal hyperplasia</td>
</tr>
<tr>
<td>adj. A</td>
<td>Adjuvant doxorubicin</td>
</tr>
<tr>
<td>AGO</td>
<td>Arbeitsgemeinschaft Gynäkologische Onkologie e.V.</td>
</tr>
<tr>
<td>AH</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>AI, AIs</td>
<td>Aromatase inhibitor(s)</td>
</tr>
<tr>
<td>ALH</td>
<td>Atypical lobular hyperplasia</td>
</tr>
<tr>
<td>A&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>Bc-spec</td>
<td>Breast cancer specific</td>
</tr>
<tr>
<td>BCS</td>
<td>Breast conserving surgery</td>
</tr>
<tr>
<td>BCSF</td>
<td>Breast cancer-free survival</td>
</tr>
<tr>
<td>BCT</td>
<td>Breast conserving therapy</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Breast International Group</td>
</tr>
<tr>
<td>bilat.</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Bip TRAM</td>
<td>Bi-pedicled TRAM</td>
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<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>
<th>Description</th>
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</thead>
<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>
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<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CHT</td>
<td>Chemotherapy</td>
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<tr>
<td>Circ.</td>
<td>Circulating</td>
</tr>
<tr>
<td>Cis / Capec</td>
<td>Cisplatin / capecitabine</td>
</tr>
<tr>
<td>CisG</td>
<td>Cisplatin / gemcitabine</td>
</tr>
<tr>
<td>CISH</td>
<td>Chromogenic in situ hybridization</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CMF</td>
<td>Cyclophosphamide / methotrexate / 5-fluorouracil</td>
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<tr>
<td>CMFP</td>
<td>CMF + prednisolon</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<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>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<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>
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<tr>
<td>DC</td>
<td>Docetaxel / cyclophosphamide</td>
</tr>
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<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
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<tr>
<td>dd</td>
<td>Dose-dense</td>
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<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>
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<tr>
<td>DOX, Doxo</td>
<td>Doxorubicin</td>
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<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 immunoassorbent 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

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

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

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

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

R0 No microscopic tumor residual
RAD Radiotherapy
rand. Pat. Patients randomized
RCT Radiochemotherapy
Rec pos Receptor positive
reg. CT + OP Regional chemotherapy and operation
Rel. Risk Relative risk
Reop Re-operation
resp. Respectively
RFA Radiofrequency ablation
RFS Recurrence-free survival
RPA Recursive partitioning analysis
RR Relative risk
RT Radiotherapy
RT-PCR Reverse transcriptase – polymerase chain reaction

S3 Highest level of evidence based guidelines according the Delphi-technique
SABCS San Antonio Breast Cancer Symposium
Scottish CTPG and ICRF Breast Unit Scottish Cancer Trials Breast Group and Imperial Cancer Research Foundation
SD Standard deviation
SERD Selective estrogen receptor down-regulator
SERM Selective estrogen receptor modulator
SF Shortening fraction
SGAP-flap Superior gluteal artery perforator-flap
signals/nucl. Signals per nucleus
SIRT Selective internal radiation therapy
SN Sentinel lymph node
SNB- Sentinel lymph node negative (not tumor infiltrated)
SNE, SLNE Sentinel lymph node excision
Solitary Meta. Solitary metastasis
Sonogr. Sonography
SPF S-phase fraction
SSM Skin-sparing mastectomy
supra-/infraclav Supraclavicular, infraclavicular
SWE Sweden
## Abbreviations – IX

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<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>
Members of the Breast Committee 1

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

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Options for Primary Prevention:
Modifiable Lifestyle Factors
Prevention

- **Version 2011**: Gerber / Thomssen
- **Version 2012–14**: Dall / Diel / Maass / Mundhenke
- **Version 2015**: Gerber / Mundhenke
Non-modifiable Risk Factors for Breast Cancer

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

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

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

- 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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Maintaining normal weight (BMI at 18.5 – 25 kg/m²)</th>
<th>Prevention/Screening and treatment of diabetes mellitus type II (reduction of breast cancer incidence and mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a B ++</td>
<td>Premenopausal</td>
<td>2b B ++</td>
</tr>
<tr>
<td>3a B ++</td>
<td>Postmenopausal</td>
<td></td>
</tr>
<tr>
<td>2a B ++</td>
<td></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)**
  - Grade: 2a, Quality: B, Recommendation: +

- **Reduced consumption of red meat**
  - Grade: 2a, Quality: B, Recommendation: +

- **Supplementation of vitamins, minerals, tracer elements**
  - Grade: 2a, Quality: B, Recommendation: -

- **Vitamin D substitution for prevention**
  - Grade: 3a, Quality: B, Recommendation: +/-

- **Vegetables / fruits**
  - Grade: 2a, Quality: B, Recommendation: +/-*

- **Phytoestrogens / Soya**
  - Grade: 2a, Quality: B, Recommendation: +/-

- **Fiber containing food**
  - Grade: 1b, Quality: A, Recommendation: +

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

- Avoiding hormonal therapy in postmenopausal women
  - Avoiding estrogen / progestin combinations
  - Avoiding estrogens only
    (no enhanced breast cancer risk with estrogen only therapy, maybe even risk reduction, but increased risk for endometrial cancer)
# Prevention
## Hormone (EGC) in der Post-MP

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MC-RR (95%CI)</th>
<th>Weitere Aussagen</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) koronare Events, 1.4 (1.1-1.9) Schlaganfälle, 2.1 (1.4-3.3) Lungenembolien, 2.1 (1.5-2.9) Thrombosen</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. Alter 67 J, keine sekundäre Prävention, Newkg. wie WHI + Cholzystektomien†</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, Art der Anwendung egal, Einnahmedauer &gt; 5 Jahre, 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 person-years</td>
<td>1.4 (1.2-1.6)</td>
<td>E-Mono, EPC &gt; E</td>
</tr>
<tr>
<td>Int J Cancer 2010</td>
<td></td>
<td>1.8 (1.4-2.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Metaanalyse</strong></td>
<td>16 Studien</td>
<td>1.21-1.40</td>
<td>Newkg. wie WHI +</td>
</tr>
<tr>
<td>Nelson HD: JAMA 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CHlebowski SABCS 2010*
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 (2/13)

Further information and references:

Screened data bases:

Screened guidelines:
ASCO (American Association of Clinical Oncology, Practice Guidelines, 2014)
CMA (Canadian Medical Association, 2014): http://www.cmaj.ca/cgi/content/full/158/3/DC1
NCCN (National Comprehensive Cancer Network, 2014):
Non Modifiable Risk Factors for Breast Cancer (3/13)

No further information

References:

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

*No further information*

**References:**

Prevention by Changing Pregnancy Related Factors (5/13)

No further information

References:


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

No further information

References:

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

No further information

References:


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

No further information

References:

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

No further information

References:

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

No further information

References:


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

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.
Prevention: Hormone (EGC) in der Post-MP (12/13)

No further information

No references
Prevention by Modifying Life Style Risk Factors: Oral contraception (13/13)

No further information

References:

Breast Cancer Risk and Prevention
Breast Cancer Risk and Prevention

- **Versions 2003–2014:**
  Schmutzler with Albert / Blohmer / Fehm / Kiechle / Maass / Mundhenke / Rody / Thomssen

- **Version 2015:**
  Schmutzler / Schmidt
Principles in Prevention

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

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

- Highest priority: „First, do no harm!“

  *(Primum nil nocere)*
Who Should be Tested for BRCA1/2 Mutations?

Oxford LoE: 2b    GR: B    AGO: ++

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

* in one side of the family

#Inclusion criteria of the German Consortium of Hereditary Breast and Ovarian Cancer (GCHBOC) based on a mutation detection rate ≥ 10% in ~17.000 families tested by 2013
BRCA1/2 Testing in Patients with TNBC (irrespective of family history)

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

Regardless of age *

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

Oxford / AGO
LoE / GR
3b C +
Recruitment of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC)

18,875 in 2014; exp. +3,000 new families in 2015

- BRCA1/2 mutation frequency: 24%
  (OC only: 35%, BC/OC: 42%)

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

*Institute for Medical Genetics, Statistics and Epidemiology, Leipzig
Suggested Use of a Screening Checklist *

Checkliste zur Erfassung einer möglichen erblichen Belastung für Brust- und/oder Eierstockkrebs

<table>
<thead>
<tr>
<th>Name der Patientin:</th>
<th>Geburtsdatum:</th>
</tr>
</thead>
</table>

### A. Patientin und deren Geschwister/Kinder

<table>
<thead>
<tr>
<th>Ausfallen</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>eines Mamma-Karzinoms bei der Patientin vor dem 36. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei der Patientin vor dem 51. LJ</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei der Patientin, das erst vor dem 51. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei der Patientin nach dem 50. LJ</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei der Patientin</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei Schwester/Töchter vor dem 36. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei Schwester/Töchtern vor dem 51. LJ</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei Schwester/Töchtern, das erst vor dem 51. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei Schwester/Töchtern nach dem 50. LJ</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei Brüdern/Söhnen</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei Schwester/Töchtern</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summe Patientin / Geschwister / Kinder**

### B. Mütterliche Linie

<table>
<thead>
<tr>
<th>Ausfallen</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erst vor dem 51. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei einem angehörigen Mann</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
<td>2</td>
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<td></td>
</tr>
</tbody>
</table>

**Summe mütterliche Linie**

### C. Väterliche Linie

<table>
<thead>
<tr>
<th>Ausfallen</th>
<th>Anzahl</th>
<th>Gewichtung</th>
<th>Ergebnis</th>
</tr>
</thead>
<tbody>
<tr>
<td>eines Mamma-Karzinoms bei einer Angehörigen vor dem 36. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines unilateralen Mamma-Karzinoms bei einer Angehörigen vor dem 51. LJ</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines bilateralen Mamma-Karzinoms bei einer Angehörigen, das erst vor dem 51. LJ</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines uni- oder bilateralen Mamma-Karzinoms bei einer Angehörigen nach dem 50. LJ</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Mamma-Karzinoms bei einem angehörigen Mann</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eines Ovarial-/Tubenkarzinoms oder einer primären Peritonealkarzinose bei einer Angehörigen</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summe väterliche Linie**

### D. Der höchste Wert aus B und C

**Scores >= 3 Punkten zu empfehlen.**

### E. Summe aus A und D = Risiko-Score

**A + D**

*online tool provided by the Ärztekammer Westfalen-Lippe based on the inclusion criteria of the GC-HBOC* 

[www.aekwl.de/brustzentren-download](http://www.aekwl.de/brustzentren-download)
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,...)

**Pie chart showing contribution of known genes to familial aggregation of breast cancer**
- BRCA1
- BRCA2
- TP53
- PTEN
- ATM
- CHEK2, BRIP1, PALB2
- Other genes
- Familial risk factors
- 79 common SNPs
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 %(^1)</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
<td>~ 25 %(^2)</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer syndrome</td>
<td>CDH1</td>
<td>~40-50 % (lobular)(^3)</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>STK11/ LKB1</td>
<td>~45-50 %(^4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: ~20 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervix: ~10 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterus: ~10 %</td>
</tr>
<tr>
<td>Lynch</td>
<td>mismatch repair MLH1, MSH2, MSH6, PMS2</td>
<td>up to twofold increased risk compared to general population(^5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial: ~ 25-60 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovary: up to 25 %</td>
</tr>
</tbody>
</table>

Recommendation: genetic counselling: GCP
Third Moderate to High Risk Gene Identified within the GC-HBOC

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

\textbf{Nature Genetics April 18, 2010}

Alfons Meindl\textsuperscript{1}, Heide Hellebrand\textsuperscript{15}, Constanze Wick\textsuperscript{2}, Verena Erven\textsuperscript{2}, Barbara Wappenschmidt\textsuperscript{3}, Dieter Niederacher\textsuperscript{4}, Marcel Freund\textsuperscript{5}, Peter Lichtner\textsuperscript{5}, Linda Hartmann\textsuperscript{6}, Heiner Schaal\textsuperscript{6}, Juliane Ramser\textsuperscript{1}, Ellen Honisch\textsuperscript{4}, Christian Kubisch\textsuperscript{7}, Hans E. Wichmann\textsuperscript{8}, Karin Kast\textsuperscript{9}, Helmut Deißler\textsuperscript{10}, Christoph Engel\textsuperscript{11}, Bertram Müller-Myhosk\textsuperscript{12}, Kornelia Neveling\textsuperscript{13}, Marion Kiechle\textsuperscript{1}, Christopher G. Mathew\textsuperscript{14}, Detlev Schindler\textsuperscript{13}, Rita K. Schmutzler\textsuperscript{3}, Helmut Hanenberg\textsuperscript{7,15}

- 1,100 BRCA1/2 negative risk families:
  - 670 breast only, 430 breast and ovarian cancer
- 6 deleterious mutations in BC/OC families only (1.5%)
## Commercially Available, Non-validated Breast Cancer Gene Panels for Risk Prediction

<table>
<thead>
<tr>
<th>Panel Name</th>
<th>Genes</th>
<th>Website Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>BROCA 40 gene panel</td>
<td>APC, ATM, BAP1, BARD1, BMPR1A, BARD2, BRCA1, BRCA2, BRIPI1, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, EPCAM, FAM175A, GALNT12, GEN1, GREM1, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PRSS1, PTEN, RAD50, RAD51C, STK11, TP53</td>
<td><a href="http://www.broca.gov">Broca.gov</a></td>
</tr>
<tr>
<td>AMBRY Genetics BreastNext</td>
<td>ATM, BAR1D, BRCA1, BRCA2, CDH1, CHEK1, CHEK2, EPCAM, FANCA, FANCC, FANCD2, FANCE, FANC, FANCG, FANCG, FANC, FANC, MEN1, MLH1, MRE11A, MSH2, MSH3, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
<td><a href="http://www.ambrygen.com">Ambrygen.com</a></td>
</tr>
<tr>
<td>CEGAT CAN02: Brust- und Ovarialkarzinom</td>
<td>ATM, BAR1D, BARD1, BMPR1A, BRCAN2A, BRCAN2B, BRIP1, CDH1, CHEK1, CHEK2, CHEK2, EPCAM, FANCA, FANC, FANCD2, FANCE, FANC, FANCG, MEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
<td><a href="http://www.cegat.de">Cegat.de</a></td>
</tr>
<tr>
<td>TruSight™ Cancer (Illumina)</td>
<td>AIP, ALK, ALK, ATM, BARD1, BMI1P1A, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH6, NBN, PALB2, PTEN, RAD50, RAD51C, STK11, TP53</td>
<td><a href="http://www.illumina.com">Illumina.com</a></td>
</tr>
<tr>
<td>CENTOGENE BC/OC panel</td>
<td>ATM, BAR1D, BARD1, BMPR1A, BRCAN2A, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, TP53</td>
<td><a href="http://www.centogene.com">Centogene.com</a></td>
</tr>
<tr>
<td>MYRIAD myRISK Panel</td>
<td>APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, TP53</td>
<td><a href="http://www.ambrygen.com">Ambrygen.com</a></td>
</tr>
</tbody>
</table>
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)
- **12** BC/OC ´research genes´ (validation in cooperation with the ENIGMA consortium)
- **8** candidate BC/OC genes (GC-HBOC, unpublished)

Strategy:

- Validation in large cohort, constant expansion and improvement
Clinical Implication:
Genotype/Phenotype

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

*Meindl et al. Nat. Genet 2010
Gevensleben et al. submitted
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
- VUS classification and clinical decision making are not standardized yet
## Low risk Variants from Genome Wide Association Studies (GWAS)

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Häufigkeit</th>
<th>TOTAL BCAC</th>
<th>FRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Odds Ratio</td>
<td>P-trend</td>
</tr>
<tr>
<td><strong>FGFR2</strong></td>
<td>rs2981582</td>
<td>38%</td>
<td>1.24</td>
<td>5x10^{-87}</td>
</tr>
<tr>
<td><strong>TOX3</strong></td>
<td>rs3803662</td>
<td>25%</td>
<td>1.21</td>
<td>8x10^{-52}</td>
</tr>
<tr>
<td>2q35</td>
<td>rs13387042</td>
<td>51%</td>
<td>1.12</td>
<td>3x10^{-34}</td>
</tr>
<tr>
<td>11q15</td>
<td>rs614367</td>
<td>15%</td>
<td>1.20</td>
<td>5x10^{-16}</td>
</tr>
<tr>
<td><strong>SLC4A7</strong></td>
<td>rs4973768</td>
<td>46%</td>
<td>1.11</td>
<td>4x10^{-23}</td>
</tr>
<tr>
<td>5p12</td>
<td>rs10941679</td>
<td>26%</td>
<td>1.12</td>
<td>4x10^{-23}</td>
</tr>
<tr>
<td><strong>MAP3K1</strong></td>
<td>rs889312</td>
<td>28%</td>
<td>1.11</td>
<td>3x10^{-20}</td>
</tr>
<tr>
<td>8q24</td>
<td>rs13281615</td>
<td>40%</td>
<td>1.10</td>
<td>8x10^{-15}</td>
</tr>
<tr>
<td><strong>CASP8</strong></td>
<td>rs1045485</td>
<td>13%</td>
<td>0.9</td>
<td>2x10^{-8}</td>
</tr>
<tr>
<td><strong>ESR1</strong></td>
<td>rs2046210</td>
<td>33%</td>
<td>1.09</td>
<td>2x10^{-15}</td>
</tr>
<tr>
<td><strong>LSP1</strong></td>
<td>rs3817198</td>
<td>30%</td>
<td>1.08</td>
<td>5x10^{-11}</td>
</tr>
<tr>
<td>1p11.2</td>
<td>rs11249433</td>
<td>39%</td>
<td>1.10</td>
<td>7x10^{-10}</td>
</tr>
<tr>
<td><strong>ZNF365</strong></td>
<td>rs10995190</td>
<td>15%</td>
<td>0.88</td>
<td>4x10^{-15}</td>
</tr>
<tr>
<td><strong>ZMIZ1</strong></td>
<td>rs704010</td>
<td>39%</td>
<td>0.92</td>
<td>3x10^{-8}</td>
</tr>
<tr>
<td><strong>CDKN2A/B</strong></td>
<td>rs1011970</td>
<td>17%</td>
<td>1.08</td>
<td>7x10^{-8}</td>
</tr>
<tr>
<td><strong>COX11</strong></td>
<td>rs6504950</td>
<td>27%</td>
<td>0.95</td>
<td>10^{-8}</td>
</tr>
<tr>
<td><strong>ANKRD16</strong></td>
<td>rs2380205</td>
<td>43%</td>
<td>0.98</td>
<td>4x10^{-7}</td>
</tr>
<tr>
<td><strong>RAD51L1</strong></td>
<td>rs999737</td>
<td>24%</td>
<td>0.94</td>
<td>2x10^{-7}</td>
</tr>
</tbody>
</table>
Low Risk Variants as Modifiers

Retrospective

Gaudet et al., in coop with GC-HBOC 2013: Combined genotype distribution of 14 variants in 8,221 BRCA2 mutation carriers (FGFR2, TOX3, 12p11, 5q11, CDKN2A/B, LSP1, 8q24, ESR1, ZNF365, 3p24, 12q24, 5p12, 11q13)

- Couch et al. in coop with the GC-HBOC 2013: Combined genotype distribution of 10 variants in 11,705 BRCA1 mutation carriers (1q32, 10q25.3, 19p13, 6q25.1, 12p11, TOX3, 2q35, LSP1, RAD51L1, TERT)

- 5% of BRCA1 carriers at lowest risk (28–50%) compared to the 5% at highest risk (81–100%)

Prospective

Mavaddat et al., 2013: combined genotype distribution of 7 low-risk SNP in 909 BRCA2 carriers

BRCA2 carriers at the highest tertile of the score distribution were at significantly higher risk than women at the lowest tertile (HR = 4.1, 95%; CI = 1.2 to 14.5; P = .02)´

first ´proof of principle´

Associations are breast cancer subtype specific

Garcia-Closas et al., Clin Cancer Res, 2008
Current Clinical Impact of Other Risk Genes

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

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

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

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

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

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Level</th>
<th>Rating</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>3b</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>
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
Non Directive Counseling for the Uptake of Preventive Measures

- According to the Genetic Diagnostic Law
- According to the Medical Devices Act, e.g. risk assessment requires professional training and expertise
- Communicate absolute risks within a manageable timeframe
- Communicate competing risks, e.g. risk of progressive disease in relation to the risk of a secondary primary in case women have already been affected by primary breast cancer
- Allow for appropriate time for consideration
Definition of Women at Moderate to High Risk

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

Oxford / AGO
LoE / GR

1a A ++

2b B +

2a B ++
## Surveillance Program for Women with Deleterious BRCA-mutations*

Multimodal intensive surveillance program lifelong

For the detection of early stage breast cancers

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age Requirement</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical breast exam</td>
<td>&gt;=25 years</td>
<td>semi-annually</td>
</tr>
<tr>
<td>Sonography</td>
<td>&gt;=25 years</td>
<td>semi-annually</td>
</tr>
<tr>
<td>Mammography</td>
<td>&gt;=40 years</td>
<td>biannual</td>
</tr>
<tr>
<td>Breast MRI (until ACR1)</td>
<td>&gt;=25 years</td>
<td>annual</td>
</tr>
</tbody>
</table>

For mortality reduction (10 year survival)

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
<th>Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>B++</td>
<td>4C+</td>
</tr>
</tbody>
</table>

*Referral to centres of the GC-HBOC or cooperating centres is recommended
Modified Surveillance Program for BRCA-neg. Women at Moderate to High Risk or Survivors of Hodgkin Disease

Rationale:

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

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

Oxford / AGO
LoE / GR

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

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

- **Risk-reducing bilateral mastectomy (RR-BM, PBM)** reduces BrCa incidence and mortality.

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

*Study participation recommended*
Risk-reducing Interventions for BRCA1/2 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)  
  **Oxford / AGO LoE / GR**
  \[2b \quad B \quad +^{*}\]

- Bilateral mastectomy + (RR-BM)
  - reduces cl BrCa incidence
  **Oxford / AGO LoE / GR**
  \[2b \quad B \quad +/^{*}\]

- Tamoxifen (reduces cl BrCa incidence)
  **Oxford / AGO LoE / GR**
  \[2b \quad B \quad +/^{*}\]

- Indication for PBM should consider age at onset of first breast cancer and the affected gene
  **Oxford / AGO LoE / GR**
  \[2a \quad B \quad +^{*}\]

+ Overall prognosis has to be considered

*Study participation recommended*
# Risk-reducing Salpingo-oophorectomy and All-cause Mortality

## Table 4. Risk-Reducing Salpingo-oophorectomy and All-Cause Mortality

<table>
<thead>
<tr>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prior Breast Cancer&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1567)</td>
<td>BRCA2 (n = 895)</td>
<td>Total (n = 1458)</td>
</tr>
<tr>
<td>Yes</td>
<td>993 (40.0)</td>
<td>706 (44.5)</td>
<td>287 (32.1)</td>
</tr>
<tr>
<td>Deaths</td>
<td>31 (3.1)</td>
<td>25 (3.5)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>No</td>
<td>1469 (60.0)</td>
<td>881 (55.5)</td>
<td>588 (67.9)</td>
</tr>
<tr>
<td>Deaths</td>
<td>146 (9.8)</td>
<td>93 (10.6)</td>
<td>53 (8.7)</td>
</tr>
</tbody>
</table>

### Age, mean (range), y

<table>
<thead>
<tr>
<th>Risk-reducing salpingo-oophorectomy</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prior Breast Cancer&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1567)</td>
<td>BRCA2 (n = 895)</td>
<td>Total (n = 1458)</td>
</tr>
<tr>
<td>Yes</td>
<td>45.4 (20.5-79.0)</td>
<td>44.5 (20.5-79.0)</td>
<td>47.6 (30.4-72.9)</td>
</tr>
<tr>
<td>No</td>
<td>39.8 (18.1-90.4)</td>
<td>38.5 (18.2-90.4)</td>
<td>41.6 (18.1-90.4)</td>
</tr>
</tbody>
</table>

### Follow-up, mean (range), y

| Age, mean (range), y | Risk-reducing salpingo-oophorectomy | All Eligible Women | No Prior Breast Cancer<sup>b</sup> | Prior Breast Cancer<sup>c</sup> |
|-------------------------------------|--------------------|----------------------------------|-------------------------------|
| Total (n = 2462) | BRCA1 (n = 1567) | BRCA2 (n = 895) | Total (n = 1458) | BRCA1 (n = 935) | BRCA2 (n = 523) | Total (n = 1027) | BRCA1 (n = 654) | BRCA2 (n = 373) |
| To death | 6.0 (0.5-23.5) | 5.9 (0.5-22.3) | 6.2 (0.5-23.5) | 9.0 (0.96-23.5) | 8.5 (1.0-22.3) | 10.3 (2.8-23.5) | 4.6 (0.5-20.3) | 4.3 (0.6-20.3) | 5.1 (0.5-13.3) |
| To censoring | 5.0 (0.5-27.9) | 5.0 (0.5-27.7) | 4.9 (0.5-27.9) | 5.8 (0.5-27.9) | 5.7 (0.5-27.9) | 5.9 (0.5-27.9) | 4.5 (0.5-24.6) | 4.8 (0.5-24.6) | 4.1 (0.5-15.4) |

### All-cause mortality after risk-reducing salpingo-oophorectomy, HR (95% CI)<sup>d</sup>

<table>
<thead>
<tr>
<th>Age ≥50 y</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prior Breast Cancer&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1567)</td>
<td>BRCA2 (n = 895)</td>
<td>Total (n = 1458)</td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td>0.40 (0.26-0.61)</td>
<td>0.38 (0.24-0.62)</td>
<td>0.52 (0.22-1.23)</td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td>0.41 (0.25-0.67)</td>
<td>0.40 (0.24-0.68)</td>
<td>0.16 (0.02-1.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age ≥50 y</th>
<th>All Eligible Women</th>
<th>No Prior Breast Cancer&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Prior Breast Cancer&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 2462)</td>
<td>BRCA1 (n = 1567)</td>
<td>BRCA2 (n = 895)</td>
<td>Total (n = 1458)</td>
</tr>
<tr>
<td>Age &lt;50 y</td>
<td>0.37 (0.15-0.94)</td>
<td>0.22 (0.06-0.85)</td>
<td>0.47 (0.12-1.80)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Values are expressed as number (percentage) unless otherwise indicated. Participants were censored at last contact.

<sup>b</sup> There were no breast cancer cases prior to risk-reducing salpingo-oophorectomy or in those who did not undergo salpingo-oophorectomy prior to the start of follow-up.

<sup>c</sup> Breast cancer allowed prior to risk-reducing salpingo-oophorectomy or start of follow-up.

<sup>d</sup> Adjusted for year of birth and stratified by center.

---

Domchek et al. JAMA 2010; Table 4.
### Contralateral Cancer Risk in 6235 BRCA1/2 Positive and Negative Patients (retrospektive)

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>BRCA negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first breast cancer &lt; 40 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>14.1 (10.1-18.0)</td>
<td>2.9 (0.0-6.3)</td>
<td>4.8 (2.6-6.9)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>30.1 (24.0-36.2)</td>
<td>18.2 (7.9-28.5)</td>
<td>10.6 (6.8-14.4)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>40.8 (33.2-48.3)</td>
<td>20.9 (9.7-32.1)</td>
<td>15.3 (10.4-20.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>55.1 (45.4-64.9)</td>
<td>38.4 (18.5-58.2)</td>
<td>28.4 (20.5-36.3)</td>
</tr>
<tr>
<td><strong>Age at first breast cancer 40-49 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>9.2 (5.8-12.5)</td>
<td>6.9 (2.7-11.1)</td>
<td>4.2 (2.9-5.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>16.7 (11.7-21.7)</td>
<td>13.4 (7.0-19.8)</td>
<td>8.4 (6.3-10.5)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>23.2 (16.9-29.6)</td>
<td>22.0 (12.1-31.9)</td>
<td>10.7 (8.1-13.3)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.5 (33.2-55.7)</td>
<td>40.5 (22.4-58.6)</td>
<td>18.1 (13.9-22.3)</td>
</tr>
<tr>
<td><strong>Age at first breast cancer ≥ 50 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>7.1 (3.8-10.5)</td>
<td>3.5 (0.9-6.1)</td>
<td>3.6 (2.7-4.5)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>11.4 (6.5-16.3)</td>
<td>10.4 (4.9-16.0)</td>
<td>5.5 (4.3-6.7)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>18.7 (11.0-26.3)</td>
<td>15.5 (7.8-23.3)</td>
<td>8.1 (6.3-9.9)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>21.6 (12.3-30.8)</td>
<td>15.5 (7.8-23.3)</td>
<td>12.9 (8.9-17.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years after first breast cancer</td>
<td>10.4 (8.3-12.5)</td>
<td>4.5 (2.5-6.5)</td>
<td>3.9 (3.2-4.6)</td>
</tr>
<tr>
<td>10 years after first breast cancer</td>
<td>20.4 (17.1-23.7)</td>
<td>13.2 (9.2-17.2)</td>
<td>7.1 (6.0-8.2)</td>
</tr>
<tr>
<td>15 years after first breast cancer</td>
<td>28.7 (24.4-32.9)</td>
<td>19.0 (13.5-24.4)</td>
<td>9.9 (8.5-11.4)</td>
</tr>
<tr>
<td>25 years after first breast cancer</td>
<td>44.1 (37.6-50.6)</td>
<td>33.5 (22.4-44.7)</td>
<td>17.2 (14.5-19.9)</td>
</tr>
</tbody>
</table>
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 mutation status is predictive for chemotherapy response 3b B +

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

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

+ Overall prognosis has to be considered

*Study participation recommended
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC

Check list (inclusion criteria)

BC

Communication, Exchange, Advice

Spec. BC

Counselling and testing

Indication for prophylactic surgery

Prophylactic surgery
Medical Prevention for Women at Increased Risk

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

• Raloxifene for postmenopausal women
  Reduction of invasive BrCa only

• AI for postmenopausal women

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

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

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

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

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

*Only proven for ER/PgR-positive primary sporadic BrCa
Breast Cancer Risk and Prevention (2/32)

Further information:

Literature from PUBMED, ASCO- and SABCS-abstracts

No references
Principles in Prevention (3/32)

No further information

No references
Who Should be Tested for BRCA1/2 Mutations? (4/32)

No further information

References:


2. German Consortium for Hereditary Breast and Ovarian Cancer, personal communication of up-dated numbers. Molecular genetic testing is recommended for the above listed families in which the mutation probability exceeds 10%.
BRCA1/2 Testing in Patients with TNBC (irrespective of family history) (5/32)

Further information:

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

References:

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

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

No further information

No references
Suggested Use of a Screening Checklist (7/32)

No further information

No references
State of the Art: Unexplained Heritability: Oligogenic Traits and Genetic Heterogeneity (8/32)

No further information

No references
Non BRCA-associated Hereditary Cancer Syndromes with Increased Risk for Breast Cancer (9/32)

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
Third Moderate to High Risk Gene Identified within the GC-HBOC (10/32)

No further information

References:


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

No further information

No references
TruRisk™ BC/OC Gene Panel (34 genes) by the German Consortium GC-HBOC (12/32)

No further information

No references
Clinical Implication: Genotype/Phenotype (13/32)

No further information

No references
Genetically Defined Subtypes are Distinct Tumor Entities (14/32)

No further information

References:


VUS: Problems and Questions (15/32)

No further information

No references
**Low Risk Variants from Genome Wide Association Studies (GWAS) (16/32)**

*No further information*

**References:**

Low Risk Variants as Modifier (17/32)

No further information

References:


Current Clinical Impact of Other Risk Genes (18/32)

No further information

References:

Requirements for the Introduction of New Diagnostic or Predictive Genetic Testing (19/32)

No further information

References:

Non Directive Counseling for the Uptake of Preventive Measures (20/32)

No further information

No references
**Definition of Women at Moderate to High Risk (21/32)**

*No further information*

**References:**


Surveillance Program for Women with deleterious BRCA-mutations (22/32)

Further information and references:


7. 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).

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.

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

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).
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.

Surgical Prevention (24/32)

No further information

References:

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

Further information and references:

2. Kauff et al NEJM 2002
3. Rebbeck et al. NEJM 2002
4. Domcheck et al. 2006
5. Meijers-Heijboer et al. 2001
6. Rebbeck et al. 2004
7. Hoogerbrugge et al. 2006
8. Domcheck et al. 2010
9. Sitzmann et al., JAMA Surg 2013

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

Prophylactic bilateral mastectomy (PBM) reduces the risk of breast cancer in BRCA1/2 mutation carriers by >95% (Meijers-Heijboer et al. NEJM 2001, Rebbeck et al. JCO 2004) and may be performed in these women after the age of 25. However, only few women opt for this intervention.
For women at high risk defined as having a heterozygote risk of >20% or a life time risk of >30% and in whom genetic analysis is not possible or not informative the beneficial effect of preventive surgery is not clear and requires an individualized strategy. Premalignant lesions of the breast develop especially over the age of 40 (Hoogerbrugge N et al. Eur J Cancer 2006). A recent cohort study proved a breast cancer specific, ovarian cancer specific and overall survival benefit for PBSO (Domchek et al. Lancet Oncology 2006).

The German Consortium for Hereditary Breast and Ovarian Cancer has developed guidelines for prophylactic surgery. Prophylactic surgery should be preceded by interdisciplinary counselling and, if possible, genetic testing within a familial breast cancer centre (addresses are deposited at www.deutsche-krebshilfe.de)
Risk-reducing Interventions for BRCA1/2 Mutation Carriers Affected by Breast Cancer (26/32)

No further information

References:

**Risk-reducing Salpingo-oophorectomy and All-cause Mortality (27/32)**

No further information

**References:**

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

No further information

No references
Therapy of BRCA1/2-associated Breast Cancer+ (29/32)

Further information:

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

References:

1. Metcalfe et al. JCO 2004
2. Pierce L. et al. JCO 2006
4. Tassone et al. BJC 2003
8. Rottenberg et al. 2008
9. Ashworth et al. JCO 2008
10. Rottenberg et al. PNAS 2008
11. Fong et al. NEJM 2009
12. Tutt et al, ASCO abst. 2009, 27(15S) CRA501
15. Robson et al. BCR 2004
Cooperation of Certified Breast Centres (BC) with Specialized Centres of the GC-HBOC (30/32)

*No further information*

*No references*
Medical Prevention for Women at Increased Risk (31/32)

No further information

References:

1. NSABP-P1 (Tamoxifen): Fischer B et al JNCI 1998
2. Star (Raloxifen): Vogel VG et al. JAMA 2006
Risk Reduction for Ipsi- and Contralateral Breast Cancer (32/32)

Further information:

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

No references
Early Detection and Diagnosis
Early Detection and Diagnosis

Versions 2005–2014:

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

Version 2015:

Schreer / Albert
### Early Detection Mammography

<table>
<thead>
<tr>
<th>Age</th>
<th>Interval</th>
<th>Oxford LOE / AGO GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>na</td>
<td>- / -</td>
</tr>
<tr>
<td>40–50</td>
<td>12–18</td>
<td>1b / B</td>
</tr>
<tr>
<td>50–70*</td>
<td>24</td>
<td>1a / A</td>
</tr>
<tr>
<td>&gt;70</td>
<td>24</td>
<td>4 / C</td>
</tr>
</tbody>
</table>

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

## Metaanalyses

<table>
<thead>
<tr>
<th>Study</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent UK Panel, 2012</strong></td>
<td></td>
</tr>
<tr>
<td>13-year metaanalysis</td>
<td>0.80 (0.73–0.89)</td>
</tr>
<tr>
<td><strong>Cochrane Review, 2011</strong></td>
<td></td>
</tr>
<tr>
<td>Fixed-effect metaanalysis of 9 RCT-trials</td>
<td>0.81 (0.74–0.87)</td>
</tr>
<tr>
<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></td>
</tr>
<tr>
<td>Women 50–59 years</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>Women 60–69 years</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td>Estimates weighted average</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Canadian Task Force, 2011</strong></td>
<td></td>
</tr>
<tr>
<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></td>
</tr>
<tr>
<td>Review of all trials and age groups</td>
<td>0.79 (0.73–0.86)</td>
</tr>
</tbody>
</table>
# Mammography Screening
## Women 40–49 Years

<table>
<thead>
<tr>
<th>RR (invited women)</th>
<th>0.74 (95%CI 0.66-0.83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–44 J</td>
<td>0.83 (95%CI 0.67-1.00)</td>
</tr>
<tr>
<td>45–49 J</td>
<td>0.68 (95%CI 0.59-0.78)</td>
</tr>
<tr>
<td>Participants</td>
<td>0.71 (95%CI 0.62-0.80)</td>
</tr>
<tr>
<td>NNS</td>
<td>1252 (95%CI 958-1915)</td>
</tr>
</tbody>
</table>

(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: 2b B ++
Elevated risk: 1b C ++
Mammographic lesion: 2b B ++
Second-look US: 2b C ++
Early Detection
Clinical Examination

As stand alone procedure

- Self-examination
- Clinical breast examination (CBE) by health professionals
- CBE because of mammo/sonographic lesion

CBE in combination with imaging

Oxford / AGO LOE / GR

1a A -*
3b C -*
5 D ++

BCP ++

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

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

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

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

* 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>Sensitivität (%)</th>
<th>Spezifität (%)</th>
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<tbody>
<tr>
<td>Kriege 2004</td>
<td>M</td>
<td>1909</td>
<td>50</td>
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<td>Warner 2004</td>
<td>M</td>
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<td>22</td>
<td>77</td>
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<td>M</td>
<td>491</td>
<td>25</td>
<td>86</td>
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<tr>
<td>Leach 2005</td>
<td>H / M</td>
<td>649</td>
<td>35</td>
<td>94</td>
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<td>Riedl 2007</td>
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<td>28</td>
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<td>85,7</td>
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<td>Kuhl 2010</td>
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<td>99,1</td>
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<td>77,4</td>
<td>89,7</td>
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<td>Sardanelli 2011</td>
<td>H / M</td>
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<td>97</td>
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<td>Gareth 2014</td>
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<td>139</td>
<td>93</td>
<td>63</td>
<td>60</td>
<td>-</td>
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</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>Assessment of benign lesions</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."

© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.
Guidelines Breast Version 2015.1
Early Detection and diagnosis (2/15)

Further information and references:

Screened data bases:
- Pubmed 2009 - 2014
- ASCO 2009 - 2014
- Cochrane 2009 - 2014
- Medline 2009 - 2014
- GIN 2009 - 2014

Guidelines:
- S3 Brustkrebsfrüherkennung
- S3 Diagnostik, Therapie, Nachsorge

Screened: Metaanalyses/ Systematic reviews / RCT / Cohort studies
**Early Detection – Mammography (3/15)**

*Further information:*

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

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

Data from observational studies and registries:
The EUROCREEN Working Group has published their report about the impact of population-based screening with mammography on breast cancer in Europe. They conclude: 1. “The best “European” estimate of of breast cancer reduction is 25-31% for women invited for screening, and 28-38% for women actually screened. The estimate of overdiagnosis range from 1-10%. The chance for saving a woman’s life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis”.
The population-based data from the United States (SEER-Cancer Statistics 1976 - 2008) showed an increase in number of early-stage breast cancer, a marginal reduction at advanced stage. The authors conclude “the imbalance suggests that there is substantial overdiagnosis, and that screening at best, only has a small effect on the rate of death from breast cancer”.

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


zurück
Breast Cancer Mortality Reduction (4/15)

No further information

References:

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

Further information:

On the basis of randomized controlled trials there is evidence of a 26% mortality reduction. The only one especially designed for this age group (“Age-Trial”) achieved a mortality reduction of 17% for those invited and 24% for those participating. These results were not yet statistically significant (95% CI, 0.66-1.04), because the follow-up time is to short for this young age group. The data have been underlined by study results of several service screening studies.

To estimate overdiagnosis within the “Age-Trial” Markov-modelling was performed and yielded the following results (Gunsoy N, 2012): “The sensitivity of mammography for invasive and in-situ breast cancers was 90% (95% CI, 72-99) and 82% (43-99), respectively. The screen-detectable mean sojourn time of preclinical non-progressive and progressive in-situ cancers was 1.3 (0.4-3.4) and 0.11 (0.05-0.19) years, respectively, and 0.8 years (0.6-1.2) for preclinical invasive breast cancer. The proportion of screen-detected in-situ cancers that were non-progressive was 55% (25-77) for the first and 40% (22-60) for subsequent screens. In our main analysis, overdiagnosis was estimated as 0.7% of screen-detected cancers. A sensitivity analysis, covering a wide range of alternative scenarios, yielded a range of 0.5% to 2.9%.” The authors conclude: “The extent of overdiagnosis due to screening in women aged 40-49 was small. Results also suggest annual screening is most suitable for women aged 40-49 in the United Kingdom due to short cancer sojourn times.”

References:


4. 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 (6/15)

Further information:

Results from the systematic review (Nothacker et al): The systematic search identified no randomized controlled trials or systematic reviews, six cohort studies of intermediate level of evidence (3b) were found. Only two of the studies included adequate follow-up of subjects with negative or benign findings. Supplemental breast ultrasound after negative mammographic screening permitted diagnosis of primarily invasive carcinomas in 0.32% of women in breast density type categories 2-4 of the American College of Radiology (ACR); mean tumor size for those identified was 9.9 mm, 90% with negative lymph node status. Most detected cancers occurred in mammographically dense breast ACR types 3 and 4. Biopsy rates were in the range 2.3%-4.7%, with PPV of 8.4-13.7% for those biopsied due to positive ultrasound, or about one third of the PPV of biopsies due to mammography. Supplemental breast ultrasound in the population of women with mammographically dense breast tissue (ACR 3 and 4) permits detection of small, otherwise occult, breast cancers. Potential adverse impacts for women in this intermediate risk group are associated with an increased biopsy rate. Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination.

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

References:


Early Detection Clinical Examination (7/15)

Further information:

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

References:

Assessment of Breast Symptoms or Lesions (8/15)

Further information:

If clinical examination, mammography and ultrasound are not conclusive, morphological diagnosis based on biopsy material is warranted. MRI has a high sensitivity but a low specificity to allow definitive diagnosis. Digital breast tomosynthesis allows an increased breast cancer detection rate and its use is recommended for screening centers in population-based trials. Shear wave elastography (SWE) is a promising adjunct to greyscale ultrasound in differentiating benign from malignant breast masses (improved specificity of breast US mass assessment without loss of sensitivity thus reducing the need for core biopsy by downstaging US-BIRADS III and IVa lesions). Automated ultrasound (ABUS/AVUS) is a potentially feasible way to meet the increasing demands for screening ultrasound in women with dense breasts as it shows a comparable diagnostic performance to hand held ultrasound examination. Minimally invasive biopsy allows definitive diagnosis in most cases at reduced expenditure. In case of suspicious microcalcifications extensively distributed in mammography several percutaneous biopsies should be performed before deciding upon mastectomy.

References:


**Tomosynthesis**


Elastography


Automated Breast Ultrasound (ABUS)
Pretherapeutic Assessment of Lesion Extension and Staging (9/15)

Further information:

Sonography corresponds better than mammography with the pathological tumor size of the invasive component of breast tumours. Mammography delineates the in situ component better if microcalcifications are present. In these cases magnification mammography is warranted. MRI is the most sensitive method for both invasive and non-invasive tumors, but lacks specificity. Thus MRI findings should be verified by percutaneous biopsy before definite treatment. The effect of MRI on the success of breast conserving therapy neither concerning short-time outcome parameter, i.e. reduction of re-excision rate nor long time outcome parameter, i.e. ipsilateral recurrence and overall survival have not been assessed in randomized studies. Therefore the overall contribution of MRI to successful breast conserving therapy cannot be assessed yet.

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

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

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

References:


8. 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


MRI: Preoperative Staging (10/15)

No further information

References:

2. Sardanelli F Overview of the role of preoperative breast MRI in the absence of evidence on patient outcomes. Breast 2010; 19: 3-6
MRI Preoperative Staging in Lobular Invasive Breast Cancer (11/15)

No further information

References:

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

No further information

No references
**MRI Screening in Women with High Familiar Risk (13/15)**

*Further information:*

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

*References:*


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

No further information

No references
MRI and DCIS (15/15)

No further information

References:

Pathology
Pathology

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

- **Version 2015:**
  Sinn / Friedrichs
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
Use of Fine Needle Aspiration Cytology*

- Nipple secretion
- Tumor
- Cyst
- Lymph node

* 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)

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

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

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

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

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

- **Full workup using step sections of ≤ 500 µm on paraffin embedded tissue**
  - Oxford / AGO LoE / GR: 5 D ++

- **Cytokeratin immunohistochemistry**
  - When suspicious, to detect micromet.
  - As a routine procedure
  - Oxford / AGO LoE / GR: 2b B ++
  - 5 D +/-

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

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

- **RT-PCR for epithelial genes**
  - OSNA
  - Oxford / AGO LoE / GR: 4 D -
  - 3b B -
Indications for Immediate Pathological Analysis Including Frozen Sections

- Sentinel node biopsy for invasive cancer
  - If clinical consequence
  - If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)
  5 D +
  5 D +/-

- Closest margin of resection
  - If macroscopically < 1 cm
  - If macroscopically > 1 cm
  5 D +
  5 D -

- Lesions ≥ 1 cm, without core biopsy
  5 D +

- Non-palpable lesions or lesions < 1 cm
  5 D --

- Asservation of fresh tissue (tumor banking)
  5 D +
Reporting: Histologic Tumor Type

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

- **Use of Nottingham grading system** (Elston & Ellis 1991) for all types of invasive breast cancer
  - Oxford LoE: 5, AGO Grade: D
  - AGO Rating: ++

- **In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used**
  - Oxford LoE: 5, AGO Grade: D
  - AGO Rating: ++

- **Grading of DCIS according to WHO-Classification, (4th ed., 2012)**
  - Oxford LoE: 5, AGO Grade: D
  - AGO Rating: ++

- **Reporting of tumor grading in numeric form (e.g. G3)**
  - Oxford LoE: 5, AGO Grade: D
  - AGO Rating: ++
Reporting: Tumor Size and Total Extent of Tumor

- Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results
  - Oxford LoE: 5, AGO GR: D, Level: ++

- Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality
  - Oxford LoE: 5, AGO GR: D, Level: ++

- Reporting of size of noninvasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2× invasive Ca)
  - Oxford LoE: 5, AGO GR: D, Level: ++
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

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

- 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 tumour cannot be assessed (e.g. tumor in multiple specimens)
### Reporting: Lymphovascular invasion

<table>
<thead>
<tr>
<th>Oxford LoE / AGO LoE</th>
<th>AGO Guidelines Breast Version 2015.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1: Lymphovascular invasion</td>
<td>5 D ++</td>
</tr>
<tr>
<td>L0: No lymphovascular invasion</td>
<td></td>
</tr>
<tr>
<td>IHC for evaluation of lymphovascular invasion</td>
<td>3b C -</td>
</tr>
<tr>
<td>Differentiation of peritumoral and extensive lymphovascular invasion</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Reporting of venous invasion (V0/V1) optional, prognostic significance not established</td>
<td>5 D +</td>
</tr>
</tbody>
</table>
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 at the invasion front

Do not consider central fibrosis and necrotic areas

Report average of lymphocytic infiltrate as percentage

Reporting: Evaluation after Neoadjuvant Chemotherapy

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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>AGO LoE / GR</th>
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<tbody>
<tr>
<td>4</td>
<td>D ++</td>
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<tr>
<td>4</td>
<td>D ++</td>
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<tr>
<td>2b</td>
<td>D +</td>
</tr>
<tr>
<td>4</td>
<td>D +/-</td>
</tr>
<tr>
<td>5</td>
<td>D ++</td>
</tr>
</tbody>
</table>
Special studies: ER-Testing by IHC

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
  
  - Reporting percentage of pos. tumor nuclei (pos. if ≥ 1%)
  
  - Staining intensity of pos. tumor nuclei (0 - 3)
  
  - Allred Score (0 - 8), Remmele Score (0 - 12)

- Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy

<table>
<thead>
<tr>
<th>Oxford / LoE / AGO</th>
<th>1a</th>
<th>A</th>
<th>++</th>
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<tbody>
<tr>
<td>Immunohistochemical detection on paraffin embedded (FFPE) tissue</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Reporting percentage of pos. tumor nuclei (pos. if ≥ 1%)</td>
<td>4</td>
<td>D</td>
<td>+</td>
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<tr>
<td>Staining intensity of pos. tumor nuclei (0 - 3)</td>
<td>4</td>
<td>D</td>
<td>+</td>
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<tr>
<td>Allred Score (0 - 8), Remmele Score (0 - 12)</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>
Special studies: PgR-Testing by IHC

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
  
  - Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%)
  
  - Staining intensity of pos. tumor nuclei (0 - 3)
  
  - Allred Score (0 - 8), Remmele Score (0 - 12)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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<tbody>
<tr>
<td>1a A ++</td>
</tr>
<tr>
<td>1a A ++</td>
</tr>
<tr>
<td>4 D +</td>
</tr>
<tr>
<td>4 D +</td>
</tr>
</tbody>
</table>
Additional special studies: Molecular analysis of ER/PgR status

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

- Evaluation of hormone receptor by RNA-sequencing
  - Oxford / AGO LoE / GR: 5 D -

- Use of molecular receptor analysis for subtyping
  - Oxford / AGO LoE / GR: 3b A +
Special studies: HER2 Testing

- **Reporting of immunohistochemistry (IHC):**
  - HER2+ if strong complete circular membrane staining of > 10% invasive cells (3+ staining pattern)
  - if > 10% circular but moderate/weak membrane staining or ≤ 10% strong staining (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**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
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: 1a A ++

- Evaluation of HER2 through using validated gene expression test kits
  - 3b B +/-

- Evaluation of HER2-amplification by RNA-sequencing
  - 5 D -

- Use of molecular HER2-testing for subtyping
  - 3b B +/-
Special studies: Evaluation of Ki-67 Score

- Counting of tumor nuclei at the invasion front
  - Oxford / LoE / AGO: 5 D ++

- Consideration of weakly stained tumor nuclei
  - Oxford / LoE / AGO: 5 D ++

- Reporting of Ki-67 positive nuclei as percentage
  - Oxford / LoE / AGO: 5 D ++

- Establishing of laboratory standards and cut-off values
  - Oxford / LoE / AGO: 5 D ++

- Use of image analysis for objective Ki-67 evaluation
  - Oxford / LoE / AGO: 5 D +
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% - 20%
- Use of standardized 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.I.2014Cochrane: Decision aids for risk communication update 2009
- EUSOMA position paper: Diagnosis of breast disease
- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition

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:

Evaluation of Sentinel Node Biopsy (10/30)

No further information

References:

Statement: Evaluation of sentinel node biopsy:


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


Statement: Frozen section


Statement: Imprint cytology instead or in addition of frozen section


Statement: RT-PCR for epithelial genes


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

No further information

References:

Statement: Sentinel node biopsy for invasive cancer


Statement: Closest margin of resection

Statement: Lesions ≥ 1 cm, without core biopsy


Statement: Non-palpable lesions or lesions < 1 cm

Reporting: Histologic Tumor Type (12/30)

No further information

References:

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

No further information

References:

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

Grading of invasive lobular carcinoma

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

No further information

References:

**Determination of tumor size**

**Multifocality**
Extensive intraductal component (EIC)


**Reporting: pTNM (15/30)**

*No further information*

**References:**

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

**pT4b category: Involvement of the skin**

**pT4d category: Inflammatory breast cancer**
Reporting: Margins of Resection and R-Classification (16/30)

No further information

References:

Pathological margin assessment

R-Classifikation
**Reporting: Lymphovascular invasion (17/30)**

*No further information*

**References:**

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

**Detection of angioinvasion**
Prognostic significance of lymphovascular invasion
**Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL) (18/30)**

No further information

**References:**

**Definition and impact of predominant lymphocytic infiltration**


Reporting: Evaluation after Neoadjuvant Chemotherapy (19/30)

No further information

References:

Specimen processing after neoadjuvant chemotherapy

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

No further information

References:

IHC-testing for ER-positivity

**IHC Scores**

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

**Low ER+ Group**
Special studies: PgR-Testing by IHC (21/30)

No further information

References:

IHC-testing for PR-positivity

Prognostic signifikance

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**

a Hellenic Cooperative Oncology Group (HeCOG) study. British Journal of Cancer, 99(11), 1775–1785. doi:10.1038/sj.bjc.6604769


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: Immunhistochemistry (30/30)

No further information

No references
Prognostic and Predictive Factors
Prognostic and Predictive Factors

- **2002–2014:**
  Costa / Friedrichs / Gerber / Göhring / Harbeck / Liedtke / Loibl / Mundhenke / Nitz / Rody / Schaller / Schmidt / Schmutzler / Schneeweiss / Simon / Solomayer / Thomssen

- **2015:**
  Fersis / Janni
Definition

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_{2001})“ 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 Element</th>
<th>A Prospective</th>
<th>B Prospective using archived samples</th>
<th>C Prospective/observational</th>
<th>D Retrospective/observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial</td>
<td>Prospective controlled trial (PCT) designed to address tumor marker</td>
<td>Prospective trial not designed to address tumor marker utility Accommodation of predictive marker requires Prospective randomized controlled trial (PRCT)</td>
<td>Prospective observational registry, treatment and follow-up not dictated</td>
<td>No prospective aspect to study</td>
</tr>
<tr>
<td>Patients and patient data</td>
<td>Prospectively enrolled, treated, and followed in PCT</td>
<td>Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest</td>
<td>Prospectively enrolled in registry, but treatment and follow-up standard of care</td>
<td>No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review</td>
</tr>
<tr>
<td>Specimen collection, processing, and archival</td>
<td>Specimens collected, processed, and assayed for specific marker in real time</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion</td>
<td>Specimens collected, processed and archived with no prospective SOPs</td>
</tr>
<tr>
<td>Statistical design and analysis</td>
<td>Study powered to address tumor marker question</td>
<td>Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays</td>
<td>Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays</td>
</tr>
<tr>
<td>Validation</td>
<td>Result unlikely to be play of chance Although preferred, validation not required</td>
<td>Result more likely to be play of chance that A but less likely than C Requires one or more validation studies</td>
<td>Result very likely to be play of chance Requires subsequent validation studies</td>
<td>Result very likely to be play of chance Requires subsequent validation</td>
</tr>
</tbody>
</table>

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

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

Requirements for a Marker-Based Test to Reach Level IB Evidence

1. Adequate amounts of archived specimen must be available from enough patients from a prospective trial ... for analyses to have adequate statistical power and for the patients included in the evaluation to be clearly representative of the patients in the trial.

2. The marker-based test should be analytically and preanalytically validated for use with archived specimens.

3. The plan for marker evaluation should be completely specified in writing before the performance of marker assays on archived specimens and should be focused on evaluation of a single completely defined marker-based test.

4. The results from archived specimens should be validated using specimens from one or more similar, but separate, studies.

McShane & Hayes, J Clin Oncol 30: 4223-4232, 2012
# Prognostic Factors I in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&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;30kg/m²)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* NACT = Neoadjuvant Chemotherapy
Reproducibility

- ER/PR discordance central vs local ≈20% (ASCO/CAP JCO 2010)

- HER2 inaccurate testing suspected in approximately 20% (ASCO/CAP JCO 2007)

- Impact of routine pathologic review in N0 BC: 20% changes: grading 40%, LVI 26%, N 15%, margin 12% (JCO 2012)

- pN0 from MIRROR study: pN0 was upstaged in 22%, pN1mi: 11% upstaged, 15% downstaged in central pathology review (Ann Oncol 2012)

- Consistency: 107 cases examined by 23 pathologists in 4 rounds: Grading: Kappa 0.53; LVI Kappa 0.38 (ECWGBSP, 1999) (Virchows Arch 1999)
Critical Issues Regarding LoEs for Biomarkers

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

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

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

## Prognostic Factors II in Early Breast Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;ox2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER / PgR</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>HER2 (IHC, FISH)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>ER / PgR / HER2 as surrogate markers for molecular subtypes</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>uPA / PAI (Femtelle® ELISA)§ 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>
<tr>
<td>Mitotic activity Index (MAI)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Provider</th>
<th>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</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>score</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></td>
<td>FFPE</td>
<td>Direct hybridization</td>
<td>no</td>
<td>prognostic postmenopausal N-/+, ER+ HER2-endocrine treated</td>
<td></td>
<td>CE-Mark FDA 510(k) Clearance</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>70 gene signature (MammaPrint®)</th>
<th>21 gene Recurrence score (Oncotype DX®)</th>
<th>8 gene signature (Endopredict®)</th>
<th>PAM 50 (Prosigna®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognosis after 5 yrs</strong> (late recurrences)</td>
<td>not separately shown</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Predictive impact (chemotherapy benefit)</strong></td>
<td>poorly validated</td>
<td>yes *</td>
<td>not shown</td>
<td>not shown</td>
</tr>
<tr>
<td><strong>Prospective-retrospective evidence (% of recruited patients)</strong></td>
<td>Multicenter validation</td>
<td>NSABP B-14 (14%) NSABP B-20 (28%) ECOG 9127 SWOG 8814 (40%) ATAC (30%)</td>
<td>ABCSG 6 (19%)</td>
<td>MA.12 (59%) MA.5 (66%) ABCSG 8 (44%) ATAC (16%)</td>
</tr>
<tr>
<td><strong>Prospective evidence (pending)</strong></td>
<td>MINDACT (completed)</td>
<td>TAILORx (n0, completed) RxPONDER (n1, ongoing)</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\textsubscript{2009}</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\textsuperscript{®})</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Therapy decisions based on CTC phenotypes</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Multigene assay (EndoPredict\textsuperscript{®}, Prosigna\textsuperscript{®}, Oncotype DX\textsuperscript{®}) \textsuperscript{§}</td>
<td>I</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>(N/-+, HR+, HER2-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 gene signature (MammaPrint\textsuperscript{®}), N0-1</td>
<td>II</td>
<td>C</td>
<td>+*</td>
</tr>
<tr>
<td>IHC4 (central pathology, published algorithm) \textsuperscript{#}</td>
<td>I</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Should only be used in selected patients if all other criteria are inconclusive for therapeutic decision making

\textsuperscript{§} Validated clinical data only available for this assay

\textsuperscript{#} Cuzick et al., J Clin Oncol 29: 4273-4278, 2011
# Neoadjuvant Systemic Chemotherapy Response Prediction I

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE\textsuperscript{2009}</th>
<th>CTS</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multigensignatur e (Mammaprint, Endopredict Oncotyp Dx, PAM50 Prosigna\textsuperscript{S})</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumour infiltrating lymphocytes</td>
<td>I</td>
<td>B</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>\textit{PIK3CA} mutation</td>
<td>II</td>
<td>B</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

\textsuperscript{S} Validierte klinische Daten nur verfügbar für diesen Assay
# 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&lt;sub&gt;OX2001&lt;/sub&gt;</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER2-Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uPA/PAI1 (Femtelle®) ELISA $</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>21 gene recurrence score (Oncotype DX®) $</td>
<td>I $</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

$ Validated clinical data only available for this assay
## Prognostic factors – Metastatic breast cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>LoE&lt;sub&gt;2009&lt;/sub&gt;</th>
<th>CTS</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulating tumor cells (CTC in blood, Cell Search®)</td>
<td>I</td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+</td>
</tr>
<tr>
<td>- Prognosis at baseline</td>
<td>I</td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</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&lt;sup&gt;a&lt;/sup&gt;</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:


Reasons given for the particular evidence level:
Statement 1 (LoE 6): ref. 2 & 3 (retrospective RCT’s, <10% Power)
Definition (3/20)

No further information

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

*Further information:*

Adjuvant chemotherapy reduces breast cancer mortality by one third. However, the benefit is closely related to the absolute risk of this individual patient. Especially in ER positive tumors one has to weigh the benefit against potentially chemotherapy-induced side effects like chronic heart failure and leucemia / MDS. Because of this, proper risk assessment is mandatory.

*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”. (1)

To improve the quality of research on biomarkers a guideline named REMARK (Reporting Recommendations of Tumor Marker Prognostic Studies) was defined. REMARK describes the informations which should be given when publishing a biomarker study such as study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. (2) Depending on the quality of a biomarker study, the Tumor Marker Utility Grading System was introduced assigning different levels of evidence to a certain marker. (3) To obtain the highest level of evidence, a marker had to be tested prospectively in a prospectively randomized clinical study. Recently a refined system for biomarker study design and evaluation that incorporates a revised level of evidence scale for tumor marker studies, including those using archived specimens, was introduced. (4) Although fully prospective randomized clinical trials to evaluate the medical utility of a prognostic or predictive biomarker are still considered the gold standard, such trials are costly, so more efficient indirect "prospective–retrospective" designs using archived specimens might reach level I
evidence if validated with consistent results. This recommendation was recently elaborated on and finally resumed by the NCCN Task Force Report for evaluation of the clinical utility of tumor markers in oncology. (5,6)

In this chapter on prognostic and predictive factors the original Oxford LoE and the revised classification of Levels of Evidence using elements of tumor marker studies as proposed by Simon, Paik and Hayes, 2009 are used as applicable.

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:

3. 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. ASCO-CAP guidelines estimate discordance between central and local pathology in about one fifth of cases for ER and PgR and HER2 status. MIRROR trialists report upgrading of N0 status by central pathological review in an comparable amount. Thus the clinician should be aware of potential problems and pitfalls when decision for adjuvant treatment is taken together with the patient.

References:


Prognostic Factors II in Early Breast Cancer (12/20)

No further information

References:

ER/PR

HER2
Ki-67


MAI


Post treatment ki 67:


SPF


uPA/PAI-1


**Commerially Available Molecular Tests (13/20) and (14/20)**

*Further information:*

Modern genomic platforms generate highly reproducible information about tumor biology, which has to be integrated during the next years to clinical routine. Since the additive clinical information is highly correlated to the validation sets the commercially available tests have been enumerated separately together with their retrospective-prospective evidence and future evidence projected for > 2015 from prospective randomized trials. ASCO- guidelines already integrated uPA/PAI1 and Oncotype DX®. German AGO members still feel that prospective evidence should be generated before general recommendation. According to the consensus (see Ärzteblatt Stellungnahme der AGO Kommission Mamma) use in selected cases is recommended.

**References:**

**Endopredict**


Mammaprint


Oncotype


PAM50


8. Sestak I, Cuzick J, Dowsett M, Filipits M, Dubsky P, Cowens W, Ferree S, Schaper C, Fesl C, Gnant M. Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of 2485 patients from the ABCSG-8 and transATAC studies using the PAM50 risk of recurrence (ROR) score SABCS 2013 (S6-04)
Prognostic Factors III in Early Breast Cancer (15/20)

No further information

References:

Adjuvant!

CTC


DTC


**Endopredict**


**IHC4**


Mammaprint


Oncotype


PAM50


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

**Further information:**

This slide is based on the evidence mainly from analyses done by GEPAR-trialists and remains widely unchanged. It helps to define those subgroups of patients who benefit from NACT in terms of downstaging/pCR. Correlations to survival parameter may differ according to individual parameters and are precised in the first slides. Ki 67 data from GEPARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations. For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs. The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEPAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

**References:**

**TIL**

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

*Further information:*

This slide is based on the evidence mainly from analyses done by GEVAR- 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 GEVARTRIO have been updated by Denkert et al. (SABCS 2012) and confirmed a strong correlation if cut-off values of ≤15 and > 35 are presumed to define low and high risk populations. For the genomic signatures there are new data from the I-Spy trial confirming the predictive value of PAM50 and Mammaprint for pCR after neoadjuvant chemotherapy and – for the first time – correlation with 3 yr dfs. The FDA Metaanalysis confirms preexisting data from neo ALLTO, Neosphere and GEVAR-trials demonstrating lower pCR rates in tumors coexpressing HR and HER2 compared to HER2+/HR-.

*References:*

TIL
Predictive Factors – Endocrine Therapy (18/20)

Further information:

EBCTCG analysis provides ample evidence that hormone receptor status is predictive for endocrine response, whereas little effect can be attributed to tumor size, nodal status, age and grading. According to the ASCO/CAP guidelines the panel recommended endocrine therapy in patients whose breast tumors show at least 1% ER positive cells. Same is true for 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.

ABCSCG12 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:


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

Further information:

Her2 overexpression (ICH, FISH) is highly predictive for anti HER2 therapy. During SABCS 2012 Baselga presented biomarker analyses evaluating patients with higher benefit from addition of pertuzumab from the CLEOPATRA trial. Neither HER2 or HER3 (mRNA), nor EGFR (mRNA) were predictive.

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

The prospectively randomized chemo N0 trial demonstrated that high levels of upA/PAI-1 are associated to increased CMF chemotherapy benefit. In N0-1/HR+ patients the 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:*


Lesions of Uncertain Malignant Potential (B3)

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

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

- **Version 2015:**
  Kreipe / Thomssen
Pathology Reporting for Minimal Invasive Biopsies

B – Classification*

B1 = unsatisfactory / normal tissue only
B2 = benign lesion
B3 = lesion of uncertain malignant potential
B4 = suspicion of malignancy
B5 = malignant

B5a = non-invasive
B5b = invasive
B5c = in-situ/invasion not assessable
B5d = non epithelial, metastatic

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

<table>
<thead>
<tr>
<th>Lesion</th>
<th>~PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>40-50%</td>
</tr>
<tr>
<td>Lobular intraepithelial Neoplasia (LN/LIN)</td>
<td>0-20%</td>
</tr>
<tr>
<td>Flat epithelial atypia (FEA)</td>
<td>15%</td>
</tr>
<tr>
<td>Radial Scar</td>
<td>3%</td>
</tr>
<tr>
<td>Complex sclerosing lesion</td>
<td>3%</td>
</tr>
<tr>
<td>Papilloma without atypia</td>
<td>0%</td>
</tr>
<tr>
<td>Cellular fibroepithelial tumors / phyllodes tumors</td>
<td>?</td>
</tr>
</tbody>
</table>
Management after Minimally Invasive Biopsy

- Interdisciplinary conference: Concordant findings in pathology and imaging?
  - yes: proceed according to histologic type 3a C ++
  - no: open biopsy 3a C ++
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

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

→ Open excisional biopsy

→ Open excisional biopsy may be omitted, with:
  a) A small lesion (≤ 2 TDLU* in vacuum biopsy) and
  b) Complete removal of imaging abnormality

**ADH at margins in resection specimen:**

→ No further surgery, if incidental finding accompanying invasive or intraductal carcinoma

---

* Oxford / AGO LoE / GR
  3a  C  ++
  5a  C  +

* Terminal ductal-lobular unit
## Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)

### Stratification of breast cancer risk*

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

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

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

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

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 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

- 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
Flat Epithelial Atypia (FEA)

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

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

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

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

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

---

* Terminal ductal-lobular unit
Papilloma

- **Includes:** central papilloma, large duct papilloma, major duct papilloma, intraductal papilloma, atypical intraductal papilloma (B3)

- To be discriminated from papilloma with DCIS and from peripheral papillomas arising in the TDLU, size ≤ 2 mm, may be multiple

- To be discriminated from intraductal papillary carcinoma and encapsulated papillary carcinoma

- **Indicator lesion:**
  May be associated with in-situ or invasive cancer (10%, in case of atypical papilloma up to 20%), increased ipsilateral risk for cancer (4.6% to 13% in case of atypical papilloma)
Strategy after Diagnosis of Central Papilloma

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

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

Papilloma at resection margin:
→ no published data available
Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radical configuration.
- Includes:
  - radial scar
  - complex sclerosing lesion (> 1 cm)
- Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)
- Risk for upgrade in open biopsy after diagnosis of radial-sclerosing lesion in core biopsy: 8.3% (79/948)*

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

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

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>3b</th>
<th>C</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radial scar / CSL in core biopsy/vacuum-assisted biopsy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open excisional biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radial scar / CSL at margins in resection specimen:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further surgery</td>
<td></td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>
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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Grade</th>
<th>LoE</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening mammography</td>
<td>5</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Women with LIN and ADH</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 +

-Raloxifen for postmenopausal women –
  Risk reduction of invasive BrCa only 1b A +/-*

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

Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1.66% in 5 years)
### Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen)

**NSABP-P1 Study, update 2005**

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

#### 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:

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Results for prior ALH, ADH, LCIS (HR AI vs Plac):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBIS.2</strong></td>
<td>Prior ADH, ALH, or LCIS Anastrozole: 154 (8.0%); Placebo: 190 (9.7%)</td>
<td>Yes (7y-BC-risk 12.1%): HR 0.31 (0.12–0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (7y-BC-risk 4.9%): HR 0.52 (0.31–0.78)</td>
</tr>
<tr>
<td><strong>MAP.3</strong></td>
<td>Prior ADH, ALH, or LCIS: Exemestane: 185 (8.1%); Placebo: 188 (8.3%)</td>
<td>Yes: HR = 0.61 (0.20–1.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No: HR = 0.26 (0.11–0.64)</td>
</tr>
</tbody>
</table>

---

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

Further information and references:

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

Pubmed Search Strategies:


Screened Guidelines:
Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
NCCN Breast cancer V.1.2014
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
National and international guidelines
Leitlinienprogramm Onkologie der AWMF, Deutschen Krebgesellschaft 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:

B3-Lesions (4/25)

Further information:

Lesions of uncertain malignant potential include atypical ductal hyperplasia (ADH), lobular neoplasia (LN), flat epithelial atypia (FEA), atypical papillary proliferations, and lesions with sampling risk because of inhomogeneity, such as phyllodes tumor, cellular fibroadenoma, and radial scars. The lesions with atypical proliferations (ADH, ALH, LCIS, FEA) are regarded both as an indicator of increased risk, but also as precursor lesions, and are part of the low-grade pathway of breast cancers [1-4]. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient, and to decide if the lesion should be excised. The recognition of atypical epithelial proliferation is based on the distinction of hyperplastic from neoplastic lesions, that is on the identification of a clonal process. As a general rule, usual type epithelial hyperplasia is morphologically and phenotypically heterogeneous, while ADH, FEA, and LN are characterized by a homogeneity of cell type and marker expression. With all types of precursor lesions, careful attention must be paid to the pathologic-radiologic correlation for the guidance of the clinical management. B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1,3% discordance for B5 lesions [5].

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% disconcordance among first and second pathology compared to 0.5-1.3% disconcordance for B5 lesions (Kreipe HH et al 2008).

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

*References:*


Statement: Indicator-/precursor lesion

Variants of Lobular Neoplasia (11/25)

Further information:

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

References:

LIN with High Risk (12/25)

Further information:

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

References:

Further information:

In contrast to atypical ductal hyperplasia, it is less clear if a follow-up excisional biopsy is beneficial to the outcome of a patient with the finding of lobular neoplasia in the core biopsy, and therefore there is some disagreement if excision should be recommended as a rule or not. This is mainly due to the relative infrequency of lobular neoplasia as the most severe finding in core biopsies and the even lower number of excisional biopsies in this situation. Not surprisingly these small studies have led to widely discrepant results and conflicting interpretations of published data. An excisional biopsy was recommended in fully developed LCIS because of an upgrade rate of greater than of 25% [1] or 16% [2], but results were inconclusive with lesions of lesser extent, namely atypical lobular hyperplasia. The argument against a routine follow-up biopsy is that LN as the most significant pathology usually is an incidental finding in an otherwise benign core biopsy and if there is no other clinical or radiological detectable lesion, it is unlikely that an excisional biopsy could yield anything more significant [3]. This argument has to be taken seriously, and at least all cases with LCIS and a mass lesion should be followed up by a surgical biopsy. However, because of the reported upgrade rates in fully developed LCIS, the nature of these lesions as non-obligate precursors, and risk of missing a radiologically occult invasive cancer, an open biopsy in classical LCIS should be considered as an option also [2], especially if multiple lobules are involved.

References:

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


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

**Flat Epithelial Atypia (FEA) (14/25)**

*Further information:*

FEA represents one of the earliest morphologically recognizable neoplastic alterations of the breast. It is characterized by mildly to severely atypical cells simply replacing the single layer of native epithelial cells in a flat fashion without appreciable proliferation.

**Marker Lesion**

FEA is highly associated with microcalcification (77%). The mammographic features are amorphous and pleomorphic microcalcification. In about one-third to one-quarter of cases of FEA seen at core biopsy, a more advanced lesion is found at excision: ADH, DCIS and 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 subtyp of B3 breast lesions and associated with noninvasive cancer but not with invasive cancer in final excision histology. Hum Pathol 2009; Epub ahead of print.
Strategy after Diagnosis of FEA (15/25)

Further information:

If a FEA is detected in core biopsy further no further (open) biopsy is indicated if the underlaying lesion / calcification is completely removed (Lee TJ, 2010). In cases of FEA combined with an ADH further surgery depends on the ADH lesion (Ingegnoli A, 2010).

Statement: FEA in core (LoE 3a)
Statement: FEA at margins in resection specimens (LoE 3b)

References:

**Papilloma (16/25)**

*Further information:*

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

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

*References:*

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:


Radially Sclerosing Lesion (18/25)

No further information

No references
Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL) (19/25)

No further information

No references
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions (20/25)

Further information:

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

References:

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 I¹, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F²
Ductal Carcinoma in Situ (DCIS)
Ductal Carcinoma in Situ
DCIS

- **Version 2002:** Gerber

- **Versions 2003–2014:** Audretsch / Brunnert / Costa / Fersis / Friedrich / Hanf / Junkermann / Lux / Maass / Möbus / Nitz / Oberhoff / Scharl / Solomayer / Souchon / Thill / Thomssen

- **Version 2015:** Blohmer / Nitz
Pretherapeutic Assessment of Suspicious Lesions (BIRADS IV)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnification view of microcalcification</td>
<td>1b A</td>
<td>++</td>
</tr>
<tr>
<td>Increase of detection rate of G1/G2 DCIS by full-field digital mammography (versus screen-film)</td>
<td>4 C</td>
<td>++</td>
</tr>
<tr>
<td>Stereotactic core needle / vacuum biopsy (VAB)</td>
<td>2b B</td>
<td>+</td>
</tr>
<tr>
<td>Specimen radiography</td>
<td>2b B</td>
<td>++</td>
</tr>
<tr>
<td>Marker (Clip) left at biopsy site for location if lesion is completely removed</td>
<td>5 D</td>
<td>++</td>
</tr>
<tr>
<td>Assessment of extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>3a C</td>
<td>+/-</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>5 D</td>
<td>++</td>
</tr>
<tr>
<td>FNA / ductal lavage</td>
<td>5 D</td>
<td>-</td>
</tr>
<tr>
<td>Interdisciplinary board presentation</td>
<td>5 D</td>
<td>++</td>
</tr>
</tbody>
</table>
## Surgical Treatment for Histologically Proven DCIS I

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excisional biopsy (wire guided)</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Bracketing wire localization in large lesions</td>
<td>5 D +</td>
</tr>
<tr>
<td>Specimen radiography</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Intraoperative ultrasound (visible lesion)</td>
<td>3a C +/-</td>
</tr>
<tr>
<td>Immediate re-excision for close margins (specimen radiography)</td>
<td>1c B ++</td>
</tr>
<tr>
<td>Intraoperative frozen section</td>
<td>5 D - -</td>
</tr>
<tr>
<td>Interdisciplinary board presentation</td>
<td>2b C ++</td>
</tr>
</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 (incl. RT)**
- **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***
  - **Mastectomy**
  - In case of DCIS in the male breast
  - BCT: ≥ 5 cm or ≥ 2.5 cm + high nuclear grade/comedonecrosis
- **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>
<th>2b</th>
<th>C</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologically clear margins (R0)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Multifocal DCIS: BCT if feasible (incl. RT)</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Re-excision required for close margin ≤ 2 mm in paraffin section</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mastectomy*</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>SNE*</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In case of DCIS in the male breast</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>BCT: ≥ 5 cm or ≥ 2.5 cm + high nuclear grade/comedonecrosis</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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*AGO e.V.*

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sowie in der DKG e.V.

Guidelines Breast
Version 2015.1

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www.ago-online.de

Further Information

References

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>C</th>
<th>++</th>
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</thead>
<tbody>
<tr>
<td>Histologically clear margins (R0)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Multifocal DCIS: BCT if feasible (incl. RT)</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Re-excision required for close margin ≤ 2 mm in paraffin section</td>
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<td>+</td>
</tr>
<tr>
<td>Mastectomy*</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>SNE*</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In case of DCIS in the male breast</td>
<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
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<td>3b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection margins</td>
<td>1a A ++</td>
</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>1a A ++</td>
</tr>
<tr>
<td>Method of diagnosis</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Focality</td>
<td>1a A ++</td>
</tr>
<tr>
<td>(mod.) Van Nuys Prognostic Index</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Palpable DCIS</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Palpable + COX-2+, p16+, Ki-67+</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Palpable + ER-, HER2+, Ki-67+</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>HER2/neu (positive vs. negative)</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>ER/PgR (positive vs. negative)</td>
<td>1a B +/-</td>
</tr>
<tr>
<td>DCIS-Score</td>
<td>2b C +/-</td>
</tr>
<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>
## 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

### Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Modality</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast conserving surgery (BCS)</td>
<td>1a</td>
<td>A ++</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>2b</td>
<td>B - -</td>
</tr>
<tr>
<td>Partial breast radiotherapy (PBI)</td>
<td>3a</td>
<td>D --</td>
</tr>
<tr>
<td>Hypofractionated radiotherapy regimens</td>
<td>2b</td>
<td>D -/+*</td>
</tr>
<tr>
<td>Radiotherapy boost on the tumor bed</td>
<td>2b</td>
<td>D --</td>
</tr>
<tr>
<td>Women younger than 45-50 years</td>
<td>2b</td>
<td>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
Goodwin A, Parker S, Ghersi D, Wilcken N.

DCIS Postoperative Systemic Treatment

- **Tamoxifen (only ER+)**
  - AI if postmenopausal and contraindication against tamoxifen

- **Other endocrine options**

- **Trastuzumab (only HER2+)**

- **For Prevention of opposite breast see Prevention chapter**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>--</td>
</tr>
</tbody>
</table>
Cochrane Analysis
Tamoxifen after DCIS (all/with Radiation)

Staley H, McCallum I, Bruce J.
Postoperative tamoxifen for ductal carcinoma in situ.

Local Recurrence of DCIS after Tumorectomy w/o Irradiation

After radiation

- Simple mastectomy
  + SN B

- 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)

No further information

No references
Pretherapeutic Assessment in Suspicious Lesions (BIRADS 4) (3/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

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


- Stereotaktische Stanzbiopsie / Vakuumbiopsie (VAB)


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


- Klinische Untersuchung
- Feinnadelpunktion / duktale Lavage
- Interdisziplinäre Tumorboard-Präsentation
Surgical Treatment for Histologically Proven DCIS I (4/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

- **Exzision (drahtmarkiert)**


- **Flankierende Drahtmarkierung bei großen Läsionen**
- **Präparatradiographie**
- **Intraoperative Sonographie (darstellbarer Befund)**

Sofortige Nachresektion bei knappen Resektionsrändern (Präparateradiographie)


Intraoperative Schnellschnittdiagnostik
Interdisziplinäre Tumorboard-Präsentation
Surgical Treatment for Histologically Proven DCIS II (5/11)

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


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

No further information

References:

- Resektionsränder
- Residualler 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**


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

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

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

- DCIS mit Mikroinvasion – Behandlung analog zum invasiven Karzinom

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

DCIS Radiotherapy (7/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung.

References:

Radiotherapie nach:

- Brusterhaltender Operation (BEO) (gesamte Brust, WBI)


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


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


**Mastektomie**


**Sonderformen der Radiotherapie:**

- **Teilbrustbestrahlung**
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, Jon david 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


Hypofractionierte Radiotherapie


Boost-RT des Tumorbettes


4. Two different hypofractionated breast radiotherapy schedules for 113 patients with ductal carcinoma in situ:

Bei Patientinnen unter 45-50 Jahren
Cochrane Analysis — Radiation after Surgery (8/11)

No further information

No references
DCIS Postoperative Systemic Treatment (9/11)

Further information:

Alle Abstimmungen mit 100% Zustimmung

References:

➢ Tamoxifen (nur ER+, nur BET)


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


Cochrane Analysis – Tamoxifen after DCIS (10/11)

No further information

No references
Local Recurrence of DCIS after Tumorectomy w/o Irradiation (11/11)

Further information and references:

Abstimmung:
Lokalrezidiv des DCIS nach Tumorektomie nach Radiatio:

Einfache Mastektomie
++ 4/19;
+ 15719

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
Breast Cancer Surgery
Oncological Aspects
Breast Cancer Surgery
Oncological Aspects

- **Versions 2002–2014:**
  Bauerfeind / Blohmer / Böhme / Costa / Fersis / Gerber / Hanf / Janni / Junkermann / Kaufmann / Kühn / Kümmel / Nitz / Rezai / Simon / Solomayer / Thomssen / Untch

- **Version 2015:**
  Thill / Rezai
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**
  
- **Mammography**
  
- **Ultrasound (breast & axilla)**
  
- **Minimalinvasive biopsy**
  
- **MRI**

---

* Oxford / AGO LoE / GR
  
5  D  ++

2b  B  ++

2b  B  ++

1c  A  +

1c  B  +/-

* No significant reduction of re-excision rate.
  The possibility of MRI guided biopsy is the precondition of breast MRI (e.g. dense breast tissue and invasive lobular cancer, suspicion of multifocal or multicentric disease)

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>5 D ++</td>
</tr>
<tr>
<td>Only recommended in high metastatic potential and / or with symptoms:</td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>5 D +</td>
</tr>
<tr>
<td>Liver ultrasound</td>
<td>5 D +</td>
</tr>
<tr>
<td>CT-scan</td>
<td>5 D +</td>
</tr>
<tr>
<td>Bone-scan</td>
<td>5 D +</td>
</tr>
<tr>
<td>FDG-PET or FDG-PET / CT</td>
<td>4 C -</td>
</tr>
<tr>
<td>Whole body MRI</td>
<td>4 C -</td>
</tr>
</tbody>
</table>
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

- Non-palpable lesion
  - Wire guided localisation
  - Radionuclide guided localisation
  - Specimen radiography or ultrasound
- Tumor-free margins required
  (also in unfavorable biology „no cells on ink“ are enough)
- Immediate intraoperative re-excision for close margins (specimen radiography and/or intra-operative pathology)
- Re-excision required for involved margins (paraffin section)
- Therapeutic stereotactic excision alone
- Ultrasound guided surgery to prevent re-excision

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

Axillary lymph node dissection indicated, but not feasible

- Radiation according to AMAROS-trial

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>To improve survival</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For staging</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>For local control</td>
<td>2a</td>
<td>A</td>
<td>+/-</td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If SLNB is possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SN + (cT1/2 cN*0; &lt; 3 SN +, BCS + tangential radiation field, no subsequent axillary radiation, adequate systemic therapy)</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>SN + (mic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SN (i+)</td>
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<td>SN + mastectomy (no radiotherapy of the chestwall)</td>
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</tr>
<tr>
<td>SN+ mastectomy (radiotherapy of the chestwall)</td>
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</tr>
<tr>
<td>Only if T1, T2 and 1-2 pos. SLN</td>
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</tbody>
</table>

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

SLNB pre or post NACT - cN0

<table>
<thead>
<tr>
<th>SLNB pre NACT</th>
<th>SLNB post NACT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0 pN0(sn)</td>
<td>cN0 pN0(sn) acc. ACOSOG Z11** criteria</td>
</tr>
<tr>
<td>ycN0</td>
<td>ycN0</td>
</tr>
<tr>
<td>ALND</td>
<td>ALND</td>
</tr>
</tbody>
</table>

Surgical Procedure according to lymph node status

<table>
<thead>
<tr>
<th>cN-status (prior therapy)</th>
<th>pN-status (prior therapy)</th>
<th>cN-status (after therapy)</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) acc. ACOSOG Z11** criteria</td>
<td>ycN0</td>
<td>ALND</td>
</tr>
<tr>
<td>cN0</td>
<td>pN+(sn) not acc. to ACOSOG Z11** criteria</td>
<td>ycN0</td>
<td>ALND</td>
</tr>
<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SNB ALND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ycN+ (CNB/FNA)</td>
<td>ALND</td>
</tr>
</tbody>
</table>

*radiocolloid and blue dye, study participation recommended

* T1/T2, BCS, 1-2 SLN pos., breast radiation
Sentinel Lymph Node Excision (SNE): Indications I

- Clinically (cN0) / sonographically neg. axilla 1b A ++
- T 1-2 2b A ++
- T 3, 4a-c 3b B +
- Multifocal / multicentric lesions 2b B +
- DCIS 3b B +/- if mastectomy is required
  - ≥ 5 cm or 2,5 cm + high grade (see DCIS)
- Male breast cancer 2b B +
- In the elderly 3b B +
- Add. FNA/CNB of LN (clinical/sonogr. suspicious) in order to enable SNE 2a B +
**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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>During pregnancy and / or breast feeding</td>
<td>3 C +</td>
</tr>
<tr>
<td>After previous tumor excision</td>
<td>2b B +</td>
</tr>
<tr>
<td>Previous major breast surgery</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>Ipsilateral breast recurrence after prior BCS and prior SNE</td>
<td>4 D +/-*</td>
</tr>
<tr>
<td>SN in the mammarian internal chain</td>
<td>2b B -</td>
</tr>
<tr>
<td>After axillary surgery</td>
<td>3b B +/-*</td>
</tr>
<tr>
<td>Prophylactic bilateral / contralateral mastectomy</td>
<td>3b B -</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>3b C +/-</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Method</th>
<th>LoE</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc Kolloid</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Blue dye</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Methylen blue</td>
<td>4</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Indocyanin green (ICG)*</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>SPIO*</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Study participation recommended

SPIO: Superparamagnetic Iron Oxide
Procedure after Neoadjuvant Therapy

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

Oxford / AGO LoE / GR

5 D ++
2b C ++
5 D ++
3b C +

Surgery after neoadjuvant chemotherapy go to chapter „Neoadjuvant chemotherapy“
## Adjuvant Therapy after Primary Surgery

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

**Without cytotoxic therapy:**

| Oxford / AGO LoE / GR |  
|-----------------------|---
| **Start irradiation 6-8 weeks after surgery** | 2b B ++ |
| **Start endocrine therapy after surgery and a.s.a.p.** | 5 D ++ |
| **Tamoxifen concurrent with radiotherapy** | 3b C + |
| **AI concurrent with radiotherapy** | 3b C + |
Breast Cancer Surgery Oncologic Aspects (2 and 3/15)

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

Update Januar 2015
Screened consensus conference:
Cochrane library:
Pretherapeutic assessment (4/15)

No further information

References:

Statement: Palpation

1. GCP

Statement: General


Statement: Mammography / Ultrasound


zurück

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 (5/15)

No further information

References:

Statement: history and physical examination

1. GCP

Statement: high metastatic potential / symptoms

Evidence of surgical procedure (6/15)

No further information

References:

Statement: lumpectomy – mastectomy


Statement: skin sparing mastectomy


Statement: Nipple sparing mastectomy


Breast conservation, surgical technical aspects (7/15)

No further information

References:


Statement: Radioguided ...


Statement: specimen radiography

Statement: tumor free margins ...

Statement: tumor free margins in intrinsic subtypes


Statement: ... re-excison ...


Statement: stereotactic excision alone ...


Statement: Intraoperative ultrasound...

Breast Conservation Surgery (8/15)

No further information

References:

Statement: Multicentricity


Statement: positive microscopic ...


Statement: Inflammatory Carcinoma


Statement: general

Axillary Lymph Node Dissection I (9/15)

No further information

References:

Statement: Axillary lymph node dissection


Statement AMAROS-trial

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

No further information

References:

Statement: Axillary lymph node dissection

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


Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy


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

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 (12/15)

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 (13/15)

No further information

References:

Statement radiotracer/blue dye:


Statement: methylene blue


Statement: ICG:


Statement: SPIO:


Statement: General


Statement: Comparisons

Procedure after neoadjuvant treatment (14/15)

No further information

References

Statement: clip marking


Statement: operation and tumor resection in new margins


Statement: tumor free margins ...

Ajuvant therapy after primary surgery (15/15)

No further information

References:

Statement: Timing of radiation and chemotherapy


Statement: Tamoxifen concurrent with chemotherapy


**Statement AI concurrent with radiotherapy**


Oncoplastic and Reconstructive Surgery
Oncoplastic and Reconstructive Surgery

- **Versions 2002–2014:**
  Audretsch / Blohmer / Brunnert / Dall / Fersis / Hanf / Kümmel / Lux / Nitz / Rezai / Rody / Scharl / Thomssen

- **Version 2015:**
  Bauerfeind / Brunnert
Definition of Oncoplastic Surgery

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

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

- Reduction mammaplasty
- Mastopexy techniques
- Oncoplastic flap techniques
- Partial mastectomy with tissue transfer

<table>
<thead>
<tr>
<th>Method</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction mammaplasty</td>
<td>2a B +</td>
</tr>
<tr>
<td>Mastopexy techniques</td>
<td>3a B +</td>
</tr>
<tr>
<td>Oncoplastic flap techniques</td>
<td>2a B +</td>
</tr>
<tr>
<td>Partial mastectomy with tissue transfer</td>
<td>3b B +</td>
</tr>
</tbody>
</table>
Algorithm of Breast Reconstruction

1st choice:
Implant-Reconstruction

Implant alone not suitable – hostile environment

TRAM-Flap or Consider implant + additional acellular matrix and / or fat grafting

LADO + implant if both not suitable

if not suitable if not suitable

Microsurgery/free flaps
# Postmastectomy Reconstruction

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford / AGO</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of silicone filled breast implants</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Autologous tissue reconstruction</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Pedicled tissue reconstruction</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Free tissue reconstruction</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Autologous tissue combined with implants</td>
<td>3a</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

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

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

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

- „Delayed-immediate“ BR

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
<th>Rating</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>3b</td>
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<td>B</td>
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<td>3b</td>
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<tr>
<td>B</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Timing of Postmastectomy Implant Reconstruction

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2a</th>
<th>B</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR without radiotherapy (RT)</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 prior to RT / following PBRT (higher complication rate)</td>
<td>2a</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>
Soft Tissue Replacement Techniques

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

* LDF = Latissimus dorsi flap

Oxford / AGO LoE / GR

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<td>3b</td>
<td>C</td>
<td>+#</td>
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<tr>
<td>2b</td>
<td>B</td>
<td>+#</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+#</td>
</tr>
</tbody>
</table>

# Participation in register studies recommended
Lipotransfer

- Lipotransfer after MX and breast reconstruction

- Lipotransfer after breast-conserving therapy

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

Oxford / AGO LoE / GR

2a B +

4 D +/-

5 D -
Reconstruction (BR) with autologous tissue

- TRAM, latissimus-dorsi-flap (both can be performed as a muscle-sparing technique)
- Delayed TRAM in risk patients
- Ipsilateral pedicled TRAM

Radiotherapy:

- BR following RT
- BR prior to RT (more fibrosis, more wound healing problems, more liponecrosis)
Free Tissue Transfer

Free tissue transfer

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

Advantage:

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

Disadvantages:

- Time- and personnel-consuming microsurgical procedure
- Intensified postoperative monitoring
- Higher rate of re-operations
- Higher total failure rate
- Pre-reconstruction RT increases rate of vascular complications
- No higher patient satisfaction than with pedicled TRAM in multivariate analysis

Oxford / AGO
LoE / GR

3a B +/-
3a B +
3a C +/-
4 C +/-
4 C +/-
Muscle-sparing techniques and accuracy of abdominal wall closure will lead to low rates of late donor site complications whatever method used.

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

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

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

Flap-implant combination
LDF* + implant
- IR following RT
- IR prior to RT

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

<table>
<thead>
<tr>
<th>Skin sparing mastectomy (SSM/NSM)</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safe (same recurrence rate as MX)</strong></td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>Higher QoL for patients</strong></td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>NAC can be preserved under special conditions</strong></td>
<td>2b B ++</td>
</tr>
<tr>
<td>- Feasible after mastopexy / reduction mammoplasty</td>
<td></td>
</tr>
</tbody>
</table>

| 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 +                |
Bilateral Risk Reducing 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. salpingoophorectomy (BSO)
- Further need for education of physicians regarding possibilities and advantages of RRBM

Oxford / AGO LoE / GR

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<tr>
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<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2a</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>3a</td>
<td>C</td>
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<tr>
<td>5</td>
<td>D</td>
<td>- -</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++*</td>
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<tr>
<td>2a</td>
<td>A</td>
<td>++*</td>
</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>

* Counselling, risk prediction and follow-up in specialised centres recommended
Types of Risk Reducing Mastectomy

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

Oxford / AGO
LoE / GR

2b B +
2b C +
2b C +
4 C +/-
Algorithm of Breast Reconstruction

1. Prophylaxis – pts at risk
2. Primary Invasive Breast Cancer
   - MX necessary or pt’s preference
3. DCIS
   - Premalignant breast disease
   - and donor sites
   - excellent - good
5. Informed Consent
   - Patient – Physician – interaction
   - Publications
6. Physical status and/or donor sites impaired
   - Local conditions fine
   - „High risk“
7. Autologous Reconstruction
8. Implant Reconstruction

Algorithm of Autologous Breast Reconstruction (1)
Algorithm of Autologous Breast Reconstruction (2)

Autologous Reconstruction

1st choice: Abdomen
No Radiation

- Small - Moderate Breast
  - Single pTRAM (MS-2)
    - or Autolog. Latissimus Dorsi

- Large Volume Breast >1000g
  - Double MS-2 pTRAM
    - or Free TRAM

- Abdomen obese >5cm
  - „Apron“ or „high risk“
    - Delay
    - CT-Angiography
    - Bip TRAM (MS-2)
    - fTRAM DIEP
Algorithm of Implant Breast Reconstruction

Premastectomy Sentinel Node Biopsy

Radiotherapy: yes or maybe

- SSM/NSM Expander/Implant
  - In case of CF: MPS-perm. Implant

No Radiotherapy

- Normal – moderate breast
  - If big skin island +/− NAC
    - SSM+E/I +Lado

- Large vol. breast
  - SSM+/-NAC E/I

Reduction pattern + Exp./Implantat

E = expander; I = implant; CF = Capsula fibrosis; MPS = micropolyurethran surface
Further information and references:

Literature research

Pubmed 2003 – 01/2015
Cochrane data base (z.B. Cochrane Breast Cancer Specialised Register)


und Thomssen et al. SOPs für die Überarbeitung der AGO-Leitlinien zum Mammakarzinom 2006 2

Verwendete Guidelines zu Diagnostik und Therapie des Mammakarzinoms:
American Association of Clinical Oncology (ASCO) and Technology Assessments:
http://www.asco.org/portal/site/ASCO/menuitem. (Practice Guidelines),
Canadian Medical Association (CMA): http://www.cmaj.ca/cgi/content/full/158/3/DC1
**Definition of oncoplastic surgery (3/21)**

*Further information:*

AGO Voting for giving a new definition 45/0

*References:*

Definition modified after: Oncoplastic techniques in breast conserving surgery
Benjamin Anderson, MD; Kristine Calhoun, MD http://www.uptodate.com/contents/oncoplastic-techniques-in-breast-conserving-surgery?source=machineLearning&search=oncoplastic+surgery&selectedTitle=1%7E1&sectionRank=1&anchor=H14027079#H14027079
**Oncoplastic breast conserving surgery (4/21)**

*Further information:*

AGO Voting for this new slide and content 45/0

*References:*

Algorithm of Breast Reconstruction (5/21)

Further information:

No voting this year

No references
Postmastectomy Reconstruction (6/21)

Further information:

Voting for this new slide and content 45/0

References:


Timing of Reconstruction (7/21)

Further information:

No voting this year

References:

Timing of Postmastectomy Implant Reconstruction (8/21)

Further information:

AGO voting for implant reconstruction before radiation:
23 voting for +
2 voting for +/-

References:

Soft tissue replacement techniques (9/21)

Further information:
Voting for new headline 45/0

References:


Lipotransfer (10/21)

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 (11/21)**

**Further information:**

Voting for whole content with one consent

**References:**

2. Qadi, Mohamud A. BS; Baltodano, Pablo A. MD; Flores, José M. MPH; Reddy, Sashank MD, PhD; Abt, Nicholas B. BS; Sarhane, Karim A. MD, MScs; Abreu, Francis M. BS; Azih, Lilian C. MD; Cooney, Carisa M. MPH; Rosson, Gedge D. MD: Are Flaps Really Better Than Implants for Breast Reconstruction in Obese Females? An Analysis of 89,514 Women Undergoing Breast Surgery from the ACS-NSQIP Database Plastic & Reconstructive Surgery: April 2014 - Volume 133 - Issue 4S - p 982–983
5. Garvey PB¹, 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 (12/21)

Further information:

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

References:

Pedicled vs. Free Tissue Transfer (13/21)

*Further information:*

No voting this year

*Reference:*

**Flap-Implant Combination (14/21)**

*Further information:*

No voting this year

*References:*


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

Further information:

No voting this year

References:


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

Further information:

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

References:

Types of Risk Reducing Mastectomy (17/21)

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

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

Further information:

No voting this year

No references
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
Adjuvant Endocrine Therapy

➢ Versions 2002–2014:

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

➢ Version 2015:

Scharl / Stickeler
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 pos. cells: endocrine responsive

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

Assessment of menopausal status

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

Standard therapy 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
  
  1a   A   ++

- Endocrine therapy sequentially after CT
  
  2b   C   ++

- Non-responsive:
  No endocrine therapy
  
  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

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

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

- **#OFS** (ovarian function suppression) 5 yrs. + TAM 5 yrs. 1b B +/-
- **#OFS 5 yrs. + AI 5 yrs.** 1b B +/-

OFS (ovarian function suppression)

* Treat as long as tolerable and premenopausal
* Switch to AI optional when patient turned postmenopausal
# Increased side effects may impair compliance. High compliance to TAM 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

- AI alone
  - Oxford / AGO LoE / GR: 1c A - -
- AI after GnRHa (induced amenorrhea)
  - Oxford / AGO LoE / GR: 5 D - -
- Upfront AI in patients with chemotherapy-induced amenorrhea (CIA, TIA)
  - Oxford / AGO LoE / GR: 4 C - -
- EAT in perimenopausal pts. with validated postmenopausal status after 5 yrs. of Tam
  - Oxford / AGO LoE / GR: 2b B +
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.

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1a</th>
<th>A</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

Ovarian Function Protection
CT + GnRHa (Interaction with CT unclear) (GnRHa application > 2 weeks prior to chemotherapy)

Impairment of CT – effect cannot be excluded!

Fertility preservation counselling

Fertility preservation with assisted reproduction therapy
Assessment of ovarian reserve in infertile patients
(>6-12 mths without conception)*

Tests for fertility assessment

- Anti-Müllerian Factor
  - Oxford / AGO LoE / GR: 5 C +

- Antral follicle count
  - Oxford / AGO LoE / GR: 3b B +/-

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

- Barrier methods
- Sterilization (tubal ligation / vasectomy)
- Non-hormonal intrauterine devices (IUDs)
- Levonorgestrel-releasing IUDs
  - Removal in newly diagnosed patients
- Timing methods
- Injectable progestin-only contraceptives
- Progestin-only oral contraceptives
- Combined oral contraceptives

Oxford / AGO LoE / GR

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

No trial included women after diagnosis of breast cancer, non-estrogen containing devices do not increase the risk to develop primary breast cancer
# Ovarian Function Preservation – Comparison of Randomized Trials

<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>Gilani*</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>Demeestre*</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>
TEXT /SOFT Joint Analysis

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

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

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

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

**Tamoxifen 20 mg/day + OFS* (n = 1016)**
- Exemestane 25 mg/day + OFS* (n = 1014)
- Tamoxifen 20 mg/day

*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

## Overview over Published Trials: Upfront and Extended Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</th>
<th>Indication</th>
<th>Pts</th>
<th>F/U mo</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>ATAC Trialists’ Group 2010</td>
<td>A</td>
<td>upfront vs T</td>
<td>6241</td>
<td>120</td>
<td>HR + patients: DFS HR 0.86, p=0.003 TTR 0.79, p=0.0002 TTDR 0.85, p=0.02</td>
<td>HR 0.87 p=0.4</td>
<td>SAE T&gt;A, 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</td>
<td>L</td>
<td>upfront² vs T</td>
<td>4922</td>
<td>97</td>
<td>DFS = 0.86 P = 0.007</td>
<td>P = 0.048</td>
<td>SAE T=L, 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, DDFS 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 Adjuvant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</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&lt;0.01 TDDR HR 0.60, p&lt;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>ABSCG6a</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></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%vs3%, 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
<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Al</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,</td>
<td></td>
<td>gyn AE T&gt;A, TE T&gt;E, SE E&gt;T, diarrhea E&gt;T, Random after 2-3y T, only pts.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ER+/u BCFS HR 0.76, ITT</td>
<td>ER+/u BCFS HR 0.75,</td>
<td></td>
<td>release-free after 2-3 y T were included</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ER+/u TTDR HR 0.83, ITT</td>
<td>TTDR HR 0.82 ER+/u,</td>
<td></td>
<td></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>DFS 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, Random after 2-3y T, only pts. release-free after 2-3 y T</td>
</tr>
<tr>
<td>ABSCG-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>DFS HR 0.60,</td>
<td></td>
<td>ns, TE T&gt;A, SE A&gt;T, Analysis of switch data only, random upfront</td>
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<tr>
<td></td>
<td>ARNO95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01 TTDR HR 0.61, p=0.01</td>
<td></td>
<td></td>
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<tr>
<td>ABSCG-08</td>
<td>Jakesz 2005</td>
<td>A</td>
<td>switch after 2y T vs T</td>
<td>2529</td>
<td>31</td>
<td>DFS HR 0.61, p=0.01</td>
<td>DFS HR 0.68,</td>
<td></td>
<td>ns, TE T&gt;A, SE A&gt;T, Analysis of switch data only, random upfront</td>
</tr>
<tr>
<td></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 %, No chemotherapy, random after 2 y T; only pts.</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 %, No chemotherapy, random after 2 y T; only pts.</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Regan et al 2011</td>
<td>L</td>
<td>switch after 2y T vs. Let switch after 2y L vs. Let.</td>
<td>1548</td>
<td>97</td>
<td>disease-free survival;</td>
<td>89-9%, 88-7%,</td>
<td></td>
<td>SE L&gt;T, VE L = T, Comparison of switch L/T or T/L vs. L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1540</td>
<td></td>
<td>85-9% ns</td>
<td>88-7%, 88-1% ns</td>
<td></td>
<td></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></td>
<td>DVT; endometrial &gt; switch Musculoskeletal problems hypolipidaemia &gt; E mono</td>
</tr>
<tr>
<td>N-SAS</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></td>
<td>dito, with heterogeneity</td>
</tr>
<tr>
<td>BC03</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years 5-9</strong></td>
<td>1.08 (0.85-1.38)</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>0.000004</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 (2/20)

No further information

No references
Assessment of Steroid Hormone Receptor Status (3/20)

No further information

References:

Statement 1
Adjuvant Endocrine Therapy – Assessment of Menopausal Status (4/20)

No further information

References:

Adjuvant Endocrine Therapy (5/20)

No further information

References:

Adjuvant Endocrine Therapy (6/20)

No further information

References:

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

Further information:

Voting: 18/7

References:


Premenopausal Patients - Adjuvant endocrine therapy (8/20)

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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade</th>
<th>Recommendation</th>
<th>Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFS (ovarian function suppression) 5 yrs. + TAM 5 yrs.</td>
<td>1b B +/-</td>
<td>Voting: 100% acceptance</td>
<td></td>
</tr>
<tr>
<td>OFS 5 yrs. + AI 5 yrs.</td>
<td>1b B +/-</td>
<td>Voting: 100% acceptance</td>
<td></td>
</tr>
</tbody>
</table>


Premenopausal Patients – Adjuvant Endocrine Therapy (9/20)

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

2. Goss PE et al: Outcomes of women who were premenopausal at diagnosis of early stage breast cancer. Cancer Res 69(Suppl.1);2009:487s(#13)
Postmenopausal patients – adjuvant endocrine therapy (10/20)

Further information and references:

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

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) (11/20)

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 (12/20)

No further information

References:

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

No further information

References:

Ovarian Function Preservation (14/20)

*No further information*

*No references*
Metaanalysis of GnRH for Prevention of Premature Ovarian Failure (15/20)

No further information

No references
TEXT/SOFT Joint Analysis (16/20)

*No further information*

*No references*
Aromatase inhibitors in Adjuvant Therapy (17/20)

No further information

No references
Aromatase inhibitors in Adjuvant Therapy – Overview over Published Trials (18/20)

*No further information*

*No references*
Assessment of Ovarian Reserve (19/20)

No further information

No references
10 Yrs versus 5 yrs Breast Cancer Mortality in ER+ (20/20)

No further information

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

- **Version 2002:** Möbus / Nitz
- **Versionen 2003–2014:** Harbeck / Jackisch / Janni / Loibl / von Minckwitz / Möbus / Müller / Nitz / Schneeweiss / Simon / Solomeyer / Stickeler / Thomssen / Untch
- **Version 2015:** Schütz / Lux
**Subtype-specific General Systemic Strategies**

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

<table>
<thead>
<tr>
<th>Subtype</th>
<th>General Systemic Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2- and “low risk”:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocrine therapy without chemotherapy</td>
</tr>
<tr>
<td>HR+/HER2- and “high risk”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conventionally dosed AT-based chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Dose dense &amp; escalated in case of high tumor burden</td>
</tr>
<tr>
<td></td>
<td>Followed by endocrine therapy</td>
</tr>
<tr>
<td>HER2+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab plus</td>
</tr>
<tr>
<td></td>
<td>Sequential A/T-based regimen with concurrent T + H</td>
</tr>
<tr>
<td></td>
<td>Anthracycline-free, carboplatinum-containing regimen</td>
</tr>
<tr>
<td></td>
<td>Dose dense &amp; escalated in case of high tumor burden</td>
</tr>
<tr>
<td>TNBC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conventionally dosed AT-based chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Dose dense &amp; escalated</td>
</tr>
</tbody>
</table>
Adjuvant Chemotherapy without Concurrent Trastuzumab: Overview

- **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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EC → P_w</strong></td>
<td>$E_{90}C$ q3w x 4 → $P_{80}$ qw1 x 12</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt; B ++</td>
</tr>
<tr>
<td><strong>DAC</strong></td>
<td>$D_{75}A_{50}C$ q3w x 6</td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>AC → P_w</strong></td>
<td>$A_{60}Cq3w$ x 4 → $P_{80}qw1$ x 12</td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>AC → D</strong></td>
<td>$A_{60}C$ q3w x 4 → $D_{100}$ qw3 x 4</td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>EC → D</strong></td>
<td>$E_{90}C$ q3w x 4 → $D_{100}$ qw3 x 4</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt; B ++</td>
</tr>
</tbody>
</table>

### Anthracycline-free regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DC</strong></td>
<td>$D_{75}C_{600}$ x4</td>
<td>1b B +</td>
</tr>
<tr>
<td><strong>Pac mono</strong></td>
<td>$P_{80}$ q1w x 12</td>
<td>1b B +/-</td>
</tr>
<tr>
<td><strong>CMF</strong></td>
<td>$C_{600}M_{40}F_{600}$ q3w x 6</td>
<td>1a A +/-</td>
</tr>
</tbody>
</table>
Dose-dense and/ or Dose-escalated Adjuvant Chemotherapy in Case of High Tumor Burden

Dose-dense regimen

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

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

- E-Pac-C q2w

* Extrapolated from doxorubicin trials
Adjuvant Chemotherapy
other Drugs

- Capecitabine containing regimen in TNBC 1a B +/-
- Platinum containing regimen in TNBC 5 D +/-
- 5- Fluorouracile added to EC/AC 1b\(^a\) A - -
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>Node-positive disease</th>
<th>Node-negative disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a A ++</td>
<td>1a A ++</td>
</tr>
<tr>
<td>2b B +</td>
<td>2b B +/-</td>
</tr>
</tbody>
</table>

Oxford / AGO
LoE / GR
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

Oxford / AGO LoE / GR

1a A ++
1b B +
1b A ++
1b A -
1b A +/-
Adjuvant Trastuzumab cardiac Monitoring for CHF

**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 $\geq 2$ kg/week

3 monthly assessment of LVEF

---

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

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

- 2b B +

---

* Study participation recommended
Adjuvant Therapy with Other Targeted Agents

- Lapatinib
  - (delayed adjuvant treatment)

- Lapatinib + Trastuzumab

- Pertuzumab

- Bevacizumab

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>(delayed adjuvant treatment)</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Lapatinib + Trastuzumab</td>
<td>1b^a</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>5</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1b^a</td>
<td>B</td>
<td>--</td>
</tr>
</tbody>
</table>
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 a B ++)**  
Vote result of the AGO recommendation: 100%


*Statement: Anthracycline/taxane based regimen*

**DAC**  
**D75A50C q3w x 6 (1b A ++)**  
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 (1ba B ++)

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


Statement: Dose-dense regimen
EC q3w / Pac q2w (1ba A+)
EC q2w / Pac q1w (1b B+)
Vote result of the AGO recommendation: 100%


Statement: Dose-dense regimen
ACPac / AC-Pac q2w (1b A+)
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-Fluorouracile added to EC/AC (1ba 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**

Vote result of the AGO recommendation: 100%


**Statements: >10 mm/> 5-10 mm/ <= 5mm**
Adjuvant treatment with Trastuzumab II (9/12)

Further information and references:

Statement: Start of treatment
Vote result of the AGO recommendation: 100%


Statement: Duration

Duration Trastuzumab 1 year
Vote result of the AGO recommendation: 100%

Duration Trastuzumab 2 year
Vote result of the AGO recommendation: 100%

**Duration Trastuzumab 0.5 years**
Vote result of the AGO recommendation: 1 +/ 23 +/- 6 -/ 1 --


Adjuvant trastuzumab – Cardia mMnitoring for CHF (10/12)

Further information and references:

Statement: Cardiac Monitoring
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

Vote result of the AGO recommendation: 100%


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

Vote result of the AGO recommendation: 100%

**Statement: with docetaxel and carboplatin**
Vote result of the AGO recommendation: 100%


**Statement: with anthracyclines**
Vote result of the AGO recommendation: 100%

See references slide 8.

**Statement: with taxanes dose-dense**
Vote result of the AGO recommendation: 100%

See references slide 8.

**Statement: radiotherapy concurrent with trastuzumab**
Vote result of the AGO recommendation: 100%

1. **M. Y. Halyard, T. M. Pisansky, L. J. Solin, L. B. Marks, L. J. Pierce, A. Dueck, E. A. Perez. Trastuzumab can be administered concurrent to adjuvant radiotherapy of the breast or thoracic wall. Adjuvant radiotherapy (RT) and trastuzumab in stage I-IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial**
Adjuvant Therapy with Other Agents (12/12)

Further information and references:

Statement: with Lapatinib
Vote result of the AGO recommendation: 100%


Statement: with Lapatinib + Trastuzumab
Vote result of the AGO recommendation: 100%

Statement: Pertuzumab
Vote result of the AGO recommendation: 100%

Trials are ongoing. No final results available.

Statement: Bevacizumab
Vote result of the AGO recommendation: 100%


Neoadjuvant (Primary) Systemic Therapy
Neoadjuvant Systemic Therapy

- **Version 2002:**
  Costa

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

- **Version 2015:**
  Friedrich / Schneeweiss
Subtype-specific General Systemic Strategies

- In case of indication for chemotherapy, consider neoadjuvant approach
  - AGO ++

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

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

- HER2+
  - Trastuzumab plus
    - Sequential A/T-based regimen with concurrent T + H
    - Anthracycline-free, carboplatin-cont. regimen
    - Dose dense & escalated in case of high tumor burden
    - ++

- TNBC
  - Conventionally dosed AT-based chemotherapy
  - Dose dense & escalated
  - Plus Carboplatin in case of family history for BC/OC or gBRCA alteration
  - +
# Neoadjuvant Systemic Chemotherapy Clinical Benefit

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

**Oxford / AGO LoE / GR**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>Grade</th>
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</thead>
<tbody>
<tr>
<td>Survival is similar after neoadjuvant therapy</td>
<td>1a</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Pathological complete response is associated with improved survival in particular subgroups</td>
<td>1b</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Can achieve operability in primary inoperable tumors</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Improved options for breast conserving surgery</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Allows individualization of therapy according to mid-course treatment effect</td>
<td>1b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>Allows individualization of post-neoadjuvant management according to refined risk assessment after neoadjuvant treatment and surgery</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
</tbody>
</table>

* Study participation recommended
## Neoadjuvant Systemic Chemotherapy Indications

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b B ++</td>
<td>Inflammatory breast cancer</td>
</tr>
<tr>
<td>1c A ++</td>
<td>Inoperable breast cancer</td>
</tr>
<tr>
<td>1b B +</td>
<td>Large operable breast cancer primarily requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation</td>
</tr>
<tr>
<td>1b A +</td>
<td>If similar postoperative adjuvant chemotherapy is indicated</td>
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</table>
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>
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<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>
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Neoadjuvant Systemic Therapy Response Prediction II

<table>
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<tr>
<th>Factor</th>
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<th>GR</th>
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<tr>
<td>Multigene signature</td>
<td>III</td>
<td>C</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>Ki-67</td>
<td>I</td>
<td>B</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tumour 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>
# Neoadjuvant Systemic Chemotherapy

## Recommended Regimens and Schedules

- **Standard regimens used in the adjuvant setting** with a duration of at least 18 weeks
  - 1a A ++

- **AC or EC → D q3w or P q1w**
  - 2b A ++

- **DAC**
  - 2b B ++

- **AP → CMF**
  - 1b A +

- **Taxane followed by anthracycline sequence**
  - 1a A +

- **Dose-dense regimen (e.g. E-P-CMF, E-P-C)**
  - 1b B +*

- **Platinum in TNBC**
  - 1a A +/-
    - In case of family history of BC/OC or BRCA alteration
    - 2b B +

---

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Regimen</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sikov WM, et al. (JCO 2015)</td>
<td>CALGB 40603 Phase II</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>
</tr>
<tr>
<td>von Minckwitz G, et al. (Lancet Oncol 2014)</td>
<td>Gepar Sixto Phase II</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>
</tr>
<tr>
<td>Ando M, et al. (BCRT 2014)</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>
</tr>
</tbody>
</table>
Neoadjuvant Systemic Chemotherapy
Recommended Methods of Monitoring of Response

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
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<tr>
<td>5</td>
<td>D</td>
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</tbody>
</table>
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: 1a B +*

- Two anti-HER2 agents without chemotherapy
  
  - Oxford / AGO LoE / GR: 2b B +/-

- Anti-HER2 agent in combination with endocrine treatment
  
  - Oxford / AGO LoE / GR: 2b C +/-

* Study participation recommended
Neoadjuvant Targeted Therapy in HER2 Negative Tumors

Bevacizumab in combination with chemotherapy

- In hormone receptor positive BC
- In TNBC
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
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 \(\rightarrow\) D x 4 or Pw x 12
  \[2b\] \[B\] +
  - DAC x 2 \(\rightarrow\) NX x 4
  \[1b\] \[B\] +

In case of progressive disease:
- Stop of NST and immediate 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
  - Oxford / AGO LoE / GR: 5D++
- Surgery
  - Oxford / AGO LoE / GR: 2bC++
- Microscopically clear margins
  - Oxford / AGO LoE / GR: 5D++
- Tumor resection in the new margins
  - Oxford / AGO LoE / GR: 3bC+
- Sentinel node biopsy
  - (see chapter “Surgery”)
Surgical Procedure of the Axilla Before or After NACT

<table>
<thead>
<tr>
<th>SLNB before or after NACT in cN0</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLNB before NACT</td>
<td>2b</td>
</tr>
<tr>
<td>SLNB after NACT</td>
<td>2a</td>
</tr>
</tbody>
</table>

Further surgical procedures depending on SLNB

<table>
<thead>
<tr>
<th>cN-Status (before NST)</th>
<th>pN-Status (before NST)</th>
<th>cN-Status (after NST)</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>pN0(sn)</td>
<td>-</td>
<td>nihil</td>
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<td>+</td>
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<td>cN0</td>
<td>pN+(sn) analogue ACOZOG</td>
<td>ycN0</td>
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<td>cN0</td>
<td>pN+(sn) not analogue ACOZOG</td>
<td>ycN0</td>
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<tr>
<td>cN+</td>
<td>cN+ (CNB/FNA)</td>
<td>ycN0</td>
<td>SNB ALND</td>
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<td>ycN+ (CNB/FNA)</td>
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</table>
Neoadjuvant Systemic Therapy
Indications for Mastectomy

- Positive margins after repeated excisions
- Radiotherapy not feasible
- In case of clinical complete response
  - Inflammatory breast cancer
  - In case of pCR
  - Multicentric lesions
  - cT4a-c breast cancer

<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
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<tbody>
<tr>
<td>3b C ++</td>
<td></td>
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<tr>
<td>5 D ++</td>
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<tr>
<td>2b C +</td>
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</tbody>
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www.ago-online.de
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 after surgery**
  2–3 weeks after surgery BCS

Oxford / AGO LoE / GR

4  C  ++

2b  B  ++
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 ++

- In case of insufficient response
  - 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)

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

### 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

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

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

Further information and references:

Systematic review of published evidence:
PUBMED 1999-2015
ASCO 1999-2015
SABCS 1999-2015
ECCO/ESMO 1999-2015
Neoadjuvant Systemic Chemotherapy - Clinical Benefit (4/20)

Further information and references:

Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0


Pathological complete response is associated with improved survival in particular subgroups
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 management according to refined risk assessment after neoadjuvant treatment and surgery
Abstimmungsergebnis der AGO-Empfehlungen: 9+, 14+/-, Rest Enthaltungen
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: 45/0


**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


AP → CMF
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**
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

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

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

2. Von Minckwitz et al. ASCO 2014 (abs 1005)
Neoadjuvant Systemic Chemotherapy Recommended Methods of Monitoring of Response (10/20)

Further information and references:

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


**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


**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 in the new margins**
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
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

In case of insufficient response further chemotherapy
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

Experimental therapies in clinical trials
Abstimmungsergebnis der AGO-Empfehlungen: 45/0

No references
**Neoadjuvant Endocrine Therapy (20/20)**

*Further information and references:*

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


**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

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

Adjuvant Radiotherapy
Adjuvant Radiotherapy (RT)

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

- **Version 2015:**
  - Thomssen / Kühn / Untch / Scharl Budach / Wenz / Souchon
Preliminary Note

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

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

- If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue colour.
Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer):
- Whole Breast Irradiation –

LoE 1b B       AGO ++

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

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.
Radiotherapy in Elderly Patients
Life Expectancy less than 10 Years

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

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

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

\[ \text{AGO}^1 \quad 1b \quad A \quad + \]

\[ \text{DEGRO}^1 \quad 1b \quad C \quad +/- \]

\[ \text{different interpretation of published data by AGO and DEGRO} \]
BCS $\geq$70y $<$4 cm cN0: Tamoxifen vs. Tamoxifen + RT
Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

<table>
<thead>
<tr>
<th>@10 yrs (95% C.I.)</th>
<th>Tamoxifen</th>
<th>Tamoxifen plus Radiotherapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local recurrence</strong></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><strong>Mastectomy-free</strong></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><strong>Distant metastasis-free</strong></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><strong>Overall survival</strong></td>
<td>66% (61% - 71%)</td>
<td>67% (62% - 72%)</td>
<td>HR=0.95 (95% CI, 0.77 to 1.18; n.s.)</td>
</tr>
</tbody>
</table>

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

- **Boost-RT** (improves local control, no survival benefit)
  - < 40 years
  - 40-60 years
  - > 60 years, if G3 or >pT1

- **Intraoperative irradiation (IORT/IOERT)**
  - As boost-irradiation followed by WBI
  - 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+)
    - IOERT

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

---

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boost-RT</td>
</tr>
<tr>
<td>&lt; 40 years</td>
</tr>
<tr>
<td>40-60 years</td>
</tr>
<tr>
<td>&gt; 60 years, if G3 or &gt;pT1</td>
</tr>
<tr>
<td>Intraoperative irradiation (IORT/IOERT)</td>
</tr>
<tr>
<td>As boost-irradiation followed by WBI</td>
</tr>
<tr>
<td>As sole radiotherapy modality</td>
</tr>
<tr>
<td>IORT using 50 kV (pT1 pN0 R0 G1-2, non-lobular, age &gt;50 y, no extensive DCIS, IORT during first surgery, HR+)</td>
</tr>
<tr>
<td>IOERT</td>
</tr>
<tr>
<td>Postoperative partial breast irradiation as sole radiotherapy modality</td>
</tr>
<tr>
<td>Interstitial brachytherapy</td>
</tr>
<tr>
<td>Intracavity balloon technique</td>
</tr>
<tr>
<td>APBI (IMRT)**</td>
</tr>
</tbody>
</table>

* Study participation recommended; **no long term data
Boost vs no Boost: EORTC 22881-10882 Trial

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

Postmastectomy Radiotherapy (PMRT)** to the Chest Wall

- > 3 tumor infiltrated lymph nodes (Lnn.)
  - Oxford / AGO LoE / GR 1a A ++
- 1–3 tumor infiltrated Lnn. high risk AGO¹ 1a A +
- 1–3 tumor infiltrated Lnn. low risk* AGO¹ 5 D +/-
- 1–3 tumor infiltrated Lnn. (every risk) DEGRO¹ 1a A +
- T3 / T4
  - pT3 pN0 R0 (and no additional risk factors) 2b B +/-
  - Oxford / AGO LoE / GR 1a A ++
- If R0 is impossible to reach (for invasive tumor) 1a A ++
- In young pts with high risk features 2b B ++
- After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d) 2a B +
  - Oxford / AGO LoE / GR 2b B +/-
  - Omission of RT if ypT0 ypN0 after NACT** 2b B +/-

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

¹ different interpretation of published data by AGO and DEGRO
*For definition of risk, go to Further information; **Study participation recommended
Radiotherapy of the Axilla

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

Oxford / AGO LoE / GR

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

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

- BCT and ACOSOG Z011-criteria fulfilled
  - No axillary treatment
  - BCT and ACOSOG Z011-criteria not met

- Mastectomy, RT of chest wall indicated and ACOSOG Z011-criteria fulfilled
  - No axillary treatment

- Mastectomy, RT of chest wall indicated or Mastectomy, RT of chest wall not planned

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

- Axillary dissection
- Radiotherapy of the axilla

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

### Supra-/infraclavicular lymphatic regions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ pN2a</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Level III involved</td>
<td>1b A ++</td>
</tr>
<tr>
<td>pN1a high risk*</td>
<td>AGO¹ 2b B +</td>
</tr>
<tr>
<td>pN1a low risk*</td>
<td>AGO¹ 2b B +/-</td>
</tr>
<tr>
<td>pN1a (every risk)</td>
<td>DEGRO¹ 2b B +</td>
</tr>
<tr>
<td>pN0 high risk, if radiotherapy of the internal mammaria lnn. chain is indicated (see below)</td>
<td>2a B +/-</td>
</tr>
<tr>
<td>After NACT/NAT (indications as for PMRT)</td>
<td>AGO¹ 2b B +/-</td>
</tr>
<tr>
<td>After NACT/NAT if cN+ (indications acc. PMRT)</td>
<td>DEGRO¹ 2b A +</td>
</tr>
</tbody>
</table>

### Internal mammaria lymph node region (IMC)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1-pN2 and HR pos. who had systemic chemoth.</td>
<td>1bᵃ B +</td>
</tr>
<tr>
<td>pN0 high risk w. centr./med. tumors (HR+, adj.CT)</td>
<td>1bᵃ B +/-</td>
</tr>
<tr>
<td>IMC-RT, if cardiac risk factors are present or if trastuzumab is given</td>
<td>2b A - -</td>
</tr>
</tbody>
</table>

¹ different interpretation of published data by AGO and DEGRO

*For definition of risk, go to Further information
Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

<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

(median follow-up 10.9 yrs)
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
Further information:

Search Strategy
Search Terms: Radiotherapy Breast Cancer
Source: Pubmed 1/2010 – 1/2015

References (Overviews):

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


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

Further information:

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

References:

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


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


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

Further information:

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

References:


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

Further information:

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

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

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

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

References:


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

Further information:

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

References:

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 >=70y <4 cm cN0: Tamoxifen vs. Tamoxifen + RT (7/15)**

*Further information:*

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

*Reference:*

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

Further information:

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

Reference:


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+/-)


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

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


Intracavity balloon technique (LoE 1b B AGO−)


APBI (IMRT) (LoE 1b B AGO−*)

Further information:

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

Reference:

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

_Further information:_

The interpretation of the current EBCTCG publication (2014) should take into account, that this meta-analysis is highly influenced by the Danish radiotherapy trials (Overgaard et al. 1997, 1999). Strong evidence on definition of low risk criteria with regard to the group of 1-3 tumor infiltrated axillary Lnn is lacking. Different definitions are discussed eg.

Kyndi et al. 2013: **Low risk** of locoregional recurrence, if at least 3 out of 4 favourable criteria are present:
- Hormone receptor receptor status positive,
- Grad I,
- HER2 negative,
- Tumor <2 cm).

Truong et al. 2005: **High risk** of locoregional recurrence
- If younger age (<45 yrs; HR=3.44) and one of the following factors:
  - High proportion of positive nodes (>25%; HR=2.00),
  - Medial tumour location (HR=2.46) or
  - Negative ER-Status (HR=2.02) and,
- If age 45+ yrs and
  - high proportion of positive nodes (>25%).

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

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


References according to the statements:

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.) (LoE 1a 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 (11/15)**

*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 (12/15)

Further information:

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

References related to the statements:

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


1-2 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 +)


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 \( \geq pN2a \) (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 Inn. chain is indicated (see below) (LoE 2a B; AGO+/-)


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


Internal mammary lymph node region (IMC)
RT to Internal mammary lymph node region (IMC) if pN1-pN2 and HR positive in patients who had systemic chemotherapy 1b\textsuperscript{a} B +


RT to Internal mammary lymph node region (IMC) if pN0 high risk with central/medial tumors 1b\textsuperscript{a} B +/-


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

No further information

References:

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

*No further information*

**References:**

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


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


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


Other compounds (bevacizumab)

Therapy Side Effects
Therapy Side Effects

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

- **Version 2015:**
  - Lück/Dall
Toxicity Assessment

Acute Toxicity
According to WHO\(^1\) or NCI-CTC\(^2\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Information required</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 none</td>
<td>organs involved</td>
</tr>
<tr>
<td>1 mild</td>
<td>type of toxicity</td>
</tr>
<tr>
<td>2 moderate</td>
<td>time interval after treatment</td>
</tr>
<tr>
<td>3 severe</td>
<td>effect on general health status</td>
</tr>
<tr>
<td>4 life threatening</td>
<td>treatment required</td>
</tr>
<tr>
<td></td>
<td>recovery achieved</td>
</tr>
</tbody>
</table>

Long-Term Toxicity
No general assessment scale

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

## Cytotoxic Anti-Cancer Drugs
### Acute Toxicity I

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haematol. Toxicity</th>
<th>Nausea/Vomit</th>
<th>Alopecia</th>
<th>Mucositis/Stomatitis</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>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
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<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
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</tr>
<tr>
<td>Cisplatin</td>
<td>+</td>
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<td>++</td>
<td></td>
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<tr>
<td>Capecitabine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Gemcitabine</td>
<td>++</td>
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<td>+</td>
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<td>+</td>
<td>++</td>
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<tr>
<td>Epi-/Doxorubicin</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pegliposomal Doxorubicin</td>
<td>+</td>
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<td>+</td>
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</tr>
<tr>
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<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>nab-Paclitaxel</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Vinorelbine</td>
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# Cytotoxic Anti-Cancer Drugs
## Acute Toxicity II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allergy</th>
<th>Neurotoxi</th>
<th>Cutane Tox</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Methotrexate</td>
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<td>+</td>
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<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>++</td>
<td></td>
<td>++</td>
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<tr>
<td>Gemcitabine</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Epi-/Doxorubicin</td>
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</tr>
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<td>Liposomal Doxo.</td>
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<td>+</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td>Mitoxantrone</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Paclitaxel</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td></td>
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<tr>
<td>nab-Paclitaxel</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
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<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine</td>
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</tr>
<tr>
<td>Eribulin</td>
<td>++</td>
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</table>

- **Cyclophosphamide**
- **Methotrexate**
- **5-Fluorouracil**
- **Carboplatin**
- **Cisplatin**
- **Capecitabine**
- **Gemcitabine**
- **Epi-/Doxorubicin**
- **Liposomal Doxo.**
- **Pegliposomal Doxo.**
- **Mitoxantrone**
- **Paclitaxel**
- **nab-Paclitaxel**
- **Docetaxel**
- **Vinorelbine**
- **Eribulin**

**Additional Notes:**
- Paravasate, Dexraxozane
- Flue-like Synd., Edema
- Paravasate, Dexraxozane
- 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 Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstrype, 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.) 2b B
- Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity 1b B
- Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently: 2b B
  - Elderly patients
  - Obesity
  - Hypertension
  - Hypercholesterolemia
  - Pre-existing cardiac diseases (incl. borderline LVEF)
  - Diabetes mellitus
- Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %) 3b C +

Oxford / AGO
LoE / GR
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**
      - LVEF drop CONFIRMED (LVEF drop ≥10% points and LVEF ≥50%)
        - STOP treatment
    - **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

Not confirmed (LVEF drop <10% points or LVEF ≥50%)
RESUME treatment
Secondary Malignancies I

- With regard to solid tumours, chemotherapy induced secondary malignancies are rare events

- Alkylating agents increase the risk of leukaemia dose-dependently to a total of 0.2–0.4% within 10 - 15 years

- Anthracycline-containing regimens increase the risk of MDS and leukaemia to 0.2–1.7% within 8 to 10 years

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

- Radiotherapy increases the risk of leukaemia by 0.2–0.4% in patients treated with anthracycline-containing chemotherapy

- Tamoxifen approximately doubles the risk for developing endometrial cancer
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
- Ovarian reserve of women who remain premenopausal after CTX is reduced
- CRA is associated with improved outcome (DFS/OS)

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

- Fatigue frequently present in breast cancer patients (30–60%)  
  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  +
Sleep disturbances are a common problem of breast cancer patients during and after therapy (20–70%).

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

Oxford / AGO LoE / GR

2a B

1b A ++
Depression is an often reported adverse event in breast cancer patients (20–30%)

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

Antidepressents have shown to improve depression in breast cancer patients

Regular exercise participation can prevent depression among breast cancer survivors
(Therapy Associated) Cognitive Impairment

- Therapy-related cognitive deficits (chemobrain frequently described (16–75%))
  - Oxford / AGO LoE / GR
  - C
- 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

<table>
<thead>
<tr>
<th></th>
<th>Visual Disturbances</th>
<th>Osteoporosis</th>
<th>Cerebro-Vascular Events</th>
<th>Fracture</th>
<th>Cardiac risk</th>
<th>Cognitive functions</th>
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<td></td>
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<tr>
<td>AI 3rd Gen*</td>
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<tr>
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<table>
<thead>
<tr>
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<th>Arthralgia Myalgia</th>
<th>Flush</th>
<th>Dysfunctional Bleeding*</th>
<th>Endometrial Changes</th>
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<tr>
<td>Goserelin</td>
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Side-Effects and Toxicity of Bone Modifying Agents (BMA) Bisphosphonates (BP) and Denosumab (DB)

- Renal function deterioration due to IV-amino-BP
- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and DB therapy (appr. 2%)
- Acute phase reaction (IV Amino-BPs, DB) 10–30%
- Gastrointestinal side effects (oral BPs) 2–10%

In adjuvant bisphosphonate therapy, major side effects were observed rarely (except APR)
Recommendations for Precautions to Prevent Osteonecrosis of the Jaw (ONJ)

Oxford LoE: 4  GR: C  AGO: +

- During bisphosphonate treatment, avoid any elective dental procedures, which involve jaw bone manipulations – if interventions are inevitable, prophylactic antibiotics are recommended (LoE 2b)

- Optimize dental status before start of bisphosphonate treatment, if feasible (LoE 2b)

- Inform patients about ONJ risk and educate about early symptom reporting

- In case of high risk for ONJ, use oral bisphosphonate

In adjuvant bisphosphonate therapy, ONJ was rare
# Frequent Side Effects of Bone Modifying Agents (BMA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Phase React.</th>
<th>Renal Tox.</th>
<th>Upper GI-SE</th>
<th>Diarrhea</th>
<th>ONJ</th>
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<td>Denusomab 120 mg sc q4w 0</td>
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<td>0</td>
<td>+</td>
<td>+</td>
<td>Hypocalcemia</td>
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Key-Toxicities – Antibodies / Antibody-drug-conjugates

Trastuzumab
- Cardiotoxicity in the adjuvant setting (0.8–4.0%) 1b A
- Troponin I might identify patients who are at risk for cardiotoxicity 2b B

Bevacizumab
- Hypertonus, proteinuria, bleeding, left ventricular dysfunction, 1a A

Pertuzumab
- Skin rash, diarrhea, mucositis 2b B

T-DM1
- Thrombocytopenia, hepatotoxicity, pyrexia, headache, pneumonitis 2b B
# Small Molecules

<table>
<thead>
<tr>
<th>Small Molecules</th>
<th>Oxford / AGO LoE / GR</th>
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</thead>
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<tr>
<td><strong>Lapatinib</strong></td>
<td>1b A</td>
</tr>
<tr>
<td>➢ Diarrhea, skin rash, fatigue</td>
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</table>

| **Everolimus**  | 2b B                  |
| ➢ Pneumonitis, stomatitis, hyperglycemia, infections, skin rash, Thrombocytopenia |                     |

| **PARP-inhibitors (olaparib)** | 3 C                  |
| ➢ Fatigue, myelosuppression    |                     |

| **cdk4/6 inhibitors (palbociclib, LEE011)** | 3 C                  |
| ➢ myelosuppression, neutropenia |                     |
**Therapy Side Effects (2/22)**

*Further information:*


Screened guidelines:

*No references*
Toxicity Assessment (3/22)

Further information:

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

Acute Toxicity according to WHO1 or NCI-CTC2:

References:

2. NCI, Bethesda, USA, Common Terminology Criteria for Adverse Events v4.0 (CTCAE; published 2010); http://evs.nci.nih.gov/ftp1/CTCAE/About.html
Cytotoxic Anti-Cancer Drugs – Acute Toxicity I (4/22)

No further information

References:

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

No further information

References:
see slide 4
No further information

No references
**Long-Term Toxicity Cardiotoxicity I (7/22)**

**Further information:**

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

**Cardiotoxicity:**

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

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

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

**French FEC:** The FASG reports ten year follow-up data in patients receiving either FE50C or FE100C from FASG 05. Delayed (> 1 month after the end of chemotherapy) symptomatic cardiotoxicity was reported in 1.5% of patients from the FE50C arm and in 1.1% of patients from the FE100C arm. In summary early and delayed cardiotoxicity was reported in 4.3% and in 4.8% of patients.
The second analysis from the FASG trials compared E+ and E- (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 af anthracyclines are used. E.g. the PACS 01 trial reported significantly lower incidence of cardiac toxicity in the 3xFEC-3xDoc arm than in the 6xFEC arm (0.4% vs. 1.3%, p=0.027). These data have been confirmed in the Cochrane analysis, where trials in which total doses of anthracycline was reduced by substitution of taxane, had subsequently less
cardiac events, than standard A-based regimens (OR=0.37 (95%CI: 0.14-0.95)). There are only limited data on cardiac safety of A-free regimens in adjuvant setting in breast cancer. Jones et al. reported 5 cardiac events in 510 patients treated by 4 cycles of AC and only 1 in 506 patients in the 4xTC arm in the US Oncology study. In the BCIRG 006 study there were also significantly less patients with >10% decrease of LVEF value in the Taxotere/Carboplatin/Herceptin (TCH) arm than in AC-TH arm (8% vs. 17.3%), although the negative synergistic cardiac effect of Herceptin should be considered separately of anthracycline cardiac side effects.

Trastuzumab and cardiac safety

Most studies have excluded elderly patients (> 60 or 65 years) or patients with other risk factors (cardiovascular diseases, obesity, hypertension) from studies including trastuzumab. In clinical practice, 32% of HER2+ EBC patients treated with trastuzumab are 'over-60'. These patients have an increased cardiovascular risk profile and develop trastuzumab related cardiotoxicity commonly. Also with regard to other risk factors there is an increased risk of trastuzumab related cardiotoxicity during treatment, which is reversible after cessation of trastuzumab.

References:

Statements
“Equivalent cardiotoxicity of doxorubicin and epirubicin at recommended dose levels (450–500 and 900–1000 mg/m² cum. dose, resp.)”
“Liposome encapsulated anthracyclines (doxorubicin) induce less cardiotoxicity”


“Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier/more frequently…”


“Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors.”


“Monitoring of cardiac function before / during / after treatment: Echocardiography (LVEF or SF in %)”


Further references:


Feasibility of Treatment Combinations Considering Toxicities (8/22)

Further information:

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

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 (9/22)

Further information:

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

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

References:


Secondary Malignancies I (10/22)

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).\(^1\)

According to the cohort data of the SEER registries 1973 to 2000 risk for second cancers was dose dependend. Radiotherapy treatment assuming standard protocol with 50Gy tumour dose and beem energy 6 MV photons. The RR were 1.45 (95%CI 1.33 to 1.58) for high dose second cancer sites (1 +Gy, lung, oesophagus, pleuro, bone and soft tissue sarcoma) with no evidence of elevated risk for sites receiving medium (05.-0,9 Gy) or low doses (< 0,5 Gy). Overall risks were generally lower for patients treated in recent years (1993 +). But the pattern of risks observed were consistend with the general literature on radiation carcinogenesis, risks were higher for sites that should have received higher doses and also higher for young age at exposure.\(^6-8\)

The risk of lung cancer was elevated for ever-smokers who receive PMRT (HR18.9, 95%CI 7.9-45.4) according the results of the nested breast cancer cohort study population of the Connecticut Tumor Registry.\(^5\)

Data are inconsistent for an elevated risk of AML/MDS after radiation exposure.\(^6-8\)

References:


Chemotherapy Related Amenorrhea (CRA) (12/22)

Further information:

Synonyma: Chemotherapy / Treatment induced Amenorrhea (TIA, CIA)
Preservation of ovarian function is an important issue in the population of breast cancer patients especially in the patient younger than 40. Up to now neither data for ovarian protection with e.g. GnRH analogues nor cryopreservation of ovarian tissue are convincing. The treatment compromising most 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 disesease-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 (Bruera et al, 2006). However, a significant effect of methylphenidate against cancer-related fatigue was confirmed in a meta-analysis performed by the Cochrane Collaboration (Peuckmann-Post et al, 2010). However the effectiveness of glucocorticoids, which are used broadly in daily praxis, has not yet been evaluated.
References:

Fatigue is frequently present...


Psycho-social interventions...


Physical exercise.....


Methylphenidate...

**(Therapy Associated) Sleeping disturbance (14/22)**

**Further information:**

Sleep disturbances are a common problem of breast cancer patients during and after therapy (20-70%) leading to disruption in women's quality of life and general ability to function (Bower, 2008; Savard et al, 2001; Ancoli-Israel et al, 2006). In a recently published study examining 823 cancer patients treated with chemotherapy, it was shown that 43% of the patients met the criteria for insomnia syndrome. Insomnia was approximately three times higher than the proportions reported in the general population. 60% of the patient sample reported that their insomnia symptoms remained unchanged from cycle 1 to cycle 2. Those with insomnia complaints had significantly more depression and fatigue than good sleepers (Palesh et al, 2010). Comorbidity, evening fatigue, and depressive symptoms predicted baseline levels of subjective sleep disturbance, and depressive symptoms predicted the trajectory of subjective sleep disturbance (Dhruva et al 2012).

New data suggest that sleep disturbances, fatigue and depression may stem from distinct TNF-a mediated inflammatory processes, especially found in chemotherapy treated patients (Bower et al, 2011, Liu et al 2012).

Empirical studies of benzodiazepines and benzodiazepine receptor antagonists indicate that they are effective in improving various aspects of sleep, although no trials have evaluated the efficacy of these medications in cancer populations. Behavioral therapies have demonstrated efficacy in the treatment of insomnia, including insomnia secondary to medical conditions, supporting their use among breast cancer patients (Berger et al, 2009). Comparative studies have shown that behavioral therapies are at least as effective and longer lasting than pharmacotherapy in treating insomnia (McChargue DE et al 2012; Berger et al. 2009). Indeed, a randomized controlled trial of behavioural therapy for women with insomnia caused or exacerbated by breast cancer found significant improvement in subjective sleep complaints, as well as improvements in mood and quality of life (Savard et al, 2005).

**References:**

Sleep disturbances are a common problem....


Behavioral therapies have demonstrated efficacy.....


(Therapy Associated) Depression (15/22)

Further information:

Depression is an often reported adverse event in breast cancer patients. The majority of studies find that 20-30% of breast cancer patients experience elevated depressive episodes (Bower, 2008), even though the occurrence of a major depressive disorder might be lower. Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time. Depression negatively affects quality of life and there is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients (Gallo et al, 2007). The occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen (Bardwell et al, 2006). Depressed mood is correlated with fatigue and sleep disturbance in the context of breast cancer. In terms of treatment psychological interventions seem to be most effective distressed patients even though these interventions do not prolong survival. Regular exercise participation and tea consumption were shown in a population-based cohort study from Shanghai to play an important role in the prevention of depression among breast cancer survivors (Chen et al, 2010). Antidepressants have also shown to improve depression, in particular paroxetine has been shown to be effective in reducing depressive symptoms in breast cancer patients, even among those who were not depressed at study entry.

References:

Statements 1-4


Reports of cognitive deficits, often referred to as chemobrain, among breast cancer patients during and after chemotherapy have been reported in 16 to 75% (Bower et al. 2008; Vardy et al. 2007; Stewart et al. 2006). Neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women and that these effects may persist for years after successful treatment (Silverman et al., 2007). A study on young premenopausal patients was able to clearly correlate chemotherapy-induced changes in cerebral white matter with impaired cognitive functioning (Deprez et al., 2011). Among breast cancer survivors who remain disease-free for more than a decade, the previous cancer treatment may further augment cognitive dysfunction associated with age-related brain changes. In patients after treatment completion there is improvement in cognitive function over time, although a subset of patients continued to show deficits for up to 10 years after treatment (Fan et al., 2005).

Interestingly, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood. In a current study examining 120 breast cancer patients treated with CMF, neuropsychological tests did not reveal any differences in cognitive function between breast cancer patients after chemotherapy and healthy controls (Debess et al., 2010). Patients rated their own cognitive functions as improved after 6 months. These results again do not support that adjuvant chemotherapy is associated with cognitive side effects in breast cancer patients. Considering adjuvant endocrine treatment, tamoxifen use was associated with statistically significant lower functioning in verbal memory and executive functioning, whereas exemestane use was not associated with statistically significant lower cognitive functioning in postmenopausal patients with breast cancer (Schilder et al., 2010).

The biologic base for these changes is unclear. However, 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.
function in patients with advanced cancer.

References:

*Therapy-related cognitive deficits (chemobrain)*...


Cognitive-behavioral therapy....


Methylphenidate might improve cognitive function....

Side-effects and Toxicity of Endocrine Agents I (17/22)

Further information:

In a metaanalysis on 19,818 pts. treated with 3rd generation aromatase inhibitors the risk of developing cardiovascular adverse events was slightly higher in comparison to tamoxifen with an RR of 1.34 translating into a minimal risk of 0.5%. (Cuppone F et al 2008)

In an actual systematic review and metaanalysis of 30,023 patients in 7 trials comparing aromatase inhibitors with tamoxifen, the increased risk for developing cardiovascular disease (OR=1.26) for aromatase inhibitors was confirmed, as well as the occurrence of bone fractures (OR=1.47), while the OR for endometrial carcinoma (OR=0.34) and venous thrombosis (OR=0.55) was significantly lower in comparison to tamoxifen (Amir et al, 2011).

References:

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 (19/22)**

*Further information:*

The reported incidence of osteonecrosis of the jaw (ONJ) ranges from 0.94% to 18.6%. A study with 1,621 patients who received 29,006 intravenous doses of BP, given monthly reported an crude ONJ incidence of 8.5%, 3.1%, and 4.9% in patients with multiple myeloma, breast cancer, and prostate cancer, respectively. Patients with breast cancer demonstrated a reduced risk for ONJ development, which turned out to be non-significant after adjustment for other variables. Multivariate analysis demonstrated that use of dentures (aOR = 2.02; 95% CI, 1.03 to 3.96), history of dental extraction (aOR = 32.97; 95% CI, 18.02 to 60.31), having ever received zoledronate (aOR = 28.09; 95% CI, 5.74 to 137.43), and each zoledronate dose (aOR = 2.02; 95% CI, 1.15 to 3.56) were associated with increased risk for ONJ development. Smoking, periodontitis, and root canal treatment did not increase risk for ONJ in patients receiving BP. In conclusion, validated dental extractions and use of dentures are risk factors for ONJ development. Ibandronate and pamidronate at the dosages and frequency used in this study seem to exhibit a safer drug profile concerning ONJ complication; however, randomized controlled trials are needed to validate these results. Before initiation of a bisphosphonate, patients should have a comprehensive dental examination.

*References:*

Frequent Side Effects of Bone Modifying Agents (BMA) (20/22)

Further information:

Side-Effects and Toxicity – Bisphosphonates

References:

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

Further information:

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

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

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

In the Phase III trial of Capecitabine with or without the oral 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:

Supportive Care
Supportive Care

- **Version 2002:**
  Diel

- **Versions 2003–2014:**
  Bauerfeind / Bischoff / Costa / Dall / Diel / Fersis / Hanf / Heinrich / Jackisch / von Minckwitz / Möbus / Oberhoff / Rody / Schaller / Scharl / Schmidt / Schütz

- **Version 2015:**
  Diel / Bischoff
Guideline Spectrum

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

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

Special emphasis is put on aspects concerning breast cancer patients.

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

In preparation: multidisciplinary guidelines of the AWMF:

„Supportive Therapie bei onkologischen Patientinnen - interdisziplinäre Querschnittsleitlinie“, announced 1.7.2012, planned release: 30.6.2015
Erythropoiesis-stimulating agents (ESAs)

- Indicated in asymptomatic anaemia
  - In dose-dense / dose-escalated CT (iddETC)

- Indicated in symptomatic anaemia
  - In the adjuvant setting
  - In the neoadjuvant/metastatic setting

- Treatment and secondary prophylaxis of chemotherapy induced anemia (CIA)

- Improvement of outcome (DFS, OS)

- Treatment start at Hb-levels approaching < 10 g/dL

- Target Hb 11–12 g/dL

- Thromboembolic events are increased with ESAs

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<td>Treatment and secondary prophylaxis of chemotherapy induced anemia</td>
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<td>Improvement of outcome (DFS, OS)</td>
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<td>Treatment start at Hb-levels approaching &lt; 10 g/dL</td>
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<td>Target Hb 11–12 g/dL</td>
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<td>Thromboembolic events are increased with ESAs</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
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
  - Prophylactic treatment in low risk patients
  - Prophylactic treatment in high risk* patients
    (e.g. according to NCCN Guidelines) with
      - Antibiotics
      - Anti-fungal agents (triazole)
      - Virostatics in solid tumors
      - Granulocyte colony-stimulating factors

* High risk 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
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 10^9

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<tr>
<th>Oxford / LoE / AGO</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b B +/-</td>
<td></td>
</tr>
<tr>
<td>3b C +</td>
<td></td>
</tr>
<tr>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>1b B ++</td>
<td></td>
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<tr>
<td>1a A +/-</td>
<td></td>
</tr>
<tr>
<td>1b A ++</td>
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<tr>
<td>1b B +</td>
<td></td>
</tr>
<tr>
<td>1b A ++</td>
<td></td>
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</tbody>
</table>
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/mm³ or expected to fall to <500 cells/mm³)

<table>
<thead>
<tr>
<th>Oxford / LoE / GR</th>
<th>Clinical examination</th>
<th>5 D ++</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily evaluation</td>
<td>5 D ++</td>
</tr>
<tr>
<td></td>
<td>Hospitalization of high risk patients</td>
<td>1b A ++</td>
</tr>
<tr>
<td></td>
<td>Homecare in low risk patients</td>
<td>1b A +</td>
</tr>
<tr>
<td></td>
<td>Differential blood count</td>
<td>5 D ++</td>
</tr>
<tr>
<td></td>
<td>Blood cultures</td>
<td>5 D ++</td>
</tr>
<tr>
<td></td>
<td>Imaging of lungs</td>
<td>3 C ++</td>
</tr>
<tr>
<td></td>
<td>Immediate initial empiric antibiotic therapy</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>Empiric antifungal therapy 4–7d in case of failure of antibiotic therapy</td>
<td>1b A ++</td>
</tr>
<tr>
<td></td>
<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 ++
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


[www.onkosupport.de](http://www.onkosupport.de)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford</th>
<th>LoE</th>
<th>AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>After assessment of emetic potential</td>
<td>5</td>
<td>D</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>of chemotherapy protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurokinin-1-receptor-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>5-HT₃-antagonists</td>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>3b</td>
<td>C</td>
<td>+</td>
<td></td>
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</tbody>
</table>
### 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><strong>Serotoninantagonisten</strong></td>
<td>Ondansetron</td>
<td>8 mg i.v., 2 x 4-8 mg p.o., transdermal</td>
<td>Kopfschmerzen, Diarrhoe, Flusshyptomatik, Transaminasenanstieg, Darmatonie in hoher Dosierung</td>
<td>sehr hoch</td>
</tr>
<tr>
<td></td>
<td>Tropisetron</td>
<td>5 mg i.v., 5 mg p.o.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Granisetron</td>
<td>1-3 mg i.v.</td>
<td></td>
<td></td>
</tr>
<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>Kopfschmerzen, Diarrhoe, Flushsymptomatik, Transaminasenanstieg, Darmatonie in hoher Dosierung</td>
<td></td>
</tr>
<tr>
<td><strong>NK 1-Antagonisten</strong></td>
<td>Aprepitant</td>
<td>125 mg d1, 80 mg d 2-3 p.o.</td>
<td>Cytochrom-P-450-Aktivierung mit Dosisreduktion von Dexamethason (2 x 8 mg), Keine Kombination mit Astemizol, Terfenadin, Cisaprid</td>
<td>sehr hoch</td>
</tr>
<tr>
<td></td>
<td>Fosaprepitant</td>
<td>150 mg d1 i.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopaminantagonisten/ substituierte Benzamide</strong></td>
<td>Metoclopramid</td>
<td>bis zu 120 mg/24h als Dauerinfusion od. als Tropfen</td>
<td>Dyskinesien (Antidot: Biperiden)</td>
<td>hoch</td>
</tr>
<tr>
<td></td>
<td>Alizaprid</td>
<td>bis zu 300 mg i.v. oder p.o./24 h (6 Amp. od. 6 Tbl.)</td>
<td>Angstreaktion, Depressionen, Diarrhoe</td>
<td>hoch</td>
</tr>
<tr>
<td><strong>Phenothiazine/ Butyrophenone</strong></td>
<td>Haloperidol</td>
<td>1-3 mg 4 x/d</td>
<td>Sedation, Senkung der Krampfschwelle, transiente Leberwerterhöhung</td>
<td>mäßig</td>
</tr>
<tr>
<td><strong>Corticosteroide</strong></td>
<td>Dexamethason</td>
<td>8-20 mg i.v. 1-3 x/d</td>
<td>Blutzuckerentgleisung, psychotische Reaktionen, Flush, Blutdruckanstieg</td>
<td>mäßig</td>
</tr>
<tr>
<td></td>
<td>Prednisolon</td>
<td>100-250 mg i.v. 1-3 x/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEPA (Netupitant and Palonosetron)</strong></td>
<td>fixe Kombinationspartner (oral)</td>
<td>NE 300 mg PA 0,5 mg</td>
<td></td>
<td>sehr hoch</td>
</tr>
</tbody>
</table>
Analgesia
(Deutsche Gesellschaft für Schmerztherapie Praxisleitlinie Tumorschmerz 2014 www.dgs-praxisleitlinien.de)

- **Non-opioids; WHO Step 1**
  Diclofenac resinate, ibuprofene and / or metamizole, paracetamole

- **Mild opioids; WHO Step 2**
  Tramadol (preferentially „retard“-formulations)
  or tilidine / naloxone (also as „retard“-formulations)

- **Strong opioids; WHO Step 3**
  Morphine, buprenorphine (sublingual or transdermal), fentanyl (transdermal), hydromorphone, oxycodone, as 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.”

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

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

1 Smith et al, J Clin Oncol 30 880-887, 2012
3 Cardoso et al, Breast 21:242-252, 2012
Supportive Care (2/22)

No further information

No references
**Guideline spectrum (3/22)**

*Further information:*

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


*No references*
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 (5/22)**

*Further information:*

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

*References:*

Relevant guidelines (6/22)

No further information

References:

Prophylaxis of Infection (7/22)

Further information:

According to relevant guidelines, antibiotic prophylaxis of asymptomatic patients under chemotherapy should be restricted to high risk cases: one selective criterion could be expected duration of neutropenia of greater than 10 days (NCCN). (ASCO absolute neutrophil count < 100/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
EORTC and ASCO G-CSF Guideline-Based FN Risk Assessment (8/22)

No further information

No references
Relevant guidelines (9/22)

No further information

References

Mucositis (10/22)

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 (11/22)

Further information:

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

In 2012, a Cochrane review sought to assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer.

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

In a comparative effectiveness study, pegfilgrastim prophylaxis was associated with a reduced risk of neutropenia-related or all-cause hospitalization relative to filgrastim prophylaxis.

A recent study demonstrated in high risk breast cancer that 6 mg lipefilgrastim, 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 (12/22)

No further information

References:

Management of Febrile Neutropenia (13/22)

Further information:

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

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

References:


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. (DGHÖ) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)
Calculated Antibiotic Therapy in FN (14/22)

Further information:

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

References:

Relevant practice guidelines:

Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der Deutschen Gesellschaft für Hämatologie und Onkologie e.V. (DGHO) www.dgho-infektionen.de (H. Link et al: erstellt 04/07)
Dexrazoxane (15/22)

Further information:

Anthracyclines are among the most active chemotherapeutic agents in cancer treatment. Although infrequent, cumulative dose-dependent cardiotoxicity is nevertheless a significant side effect of this therapy resulting in reduced cardiac reserve or even frank cardiac failure. Although used in several types of malignancy, anthracyclines are most commonly used in breast cancer treatment. Importantly, recent advances have also seen the increasing use of another cardiotoxic agent, the monoclonal antibody trastuzumab, both in the metastatic as well as in the adjuvant breast cancer setting. A great number of studies review and discusses the relationship of cardiotoxicity and anthracycline use, particularly in the breast cancer setting, and explores available treatment options for the anthracycline-treated patients based on evidence from recent Phase III trials.

Dexrazoxane is not recommended for routine use in breast cancer (BC) in adjuvant setting, or metastatic setting with initial doxorubicin-based chemotherapy. Consider use with metastatic BC and other malignancies, for patients who have received more than 300 mg/m² doxorubicin who may benefit from continued doxorubicin-containing therapy. Cardiac monitoring should continue in patients receiving doxorubicin.

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

References:


**Paravasation Dexrazoxane (16/22)**

Further information:

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

References:

Relevant practice guideline

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

Witte J, de Wit M.
Prävention, Diagnostik und Therapie der zytostatikaassoziierten Paravasation - Was tun wenn's brennt?
Im Focus Onkologie 2010;6:50-55.
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 glycocorticoids on nonhematologic malignancy BMC Cancer (2008); 8:84


7. Massa E, Astara G, Madeddu C, Dessì M, Loi C, Lepori S, Mantovani G. Palonosetron plus dexamethasone effectively prevents acute and delayed chemotherapy-induced nausea and vomiting following highly or moderately emetogenic chemotherapy in pre-treated patients who have failed to respond to a previous antiemetic treatment: Comparison between elderly and non-elderly patient response. Crit Rev Oncol Hematol. 2008 Aug 23. [Epub ahead of print]


**Relevant 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 (18/22)

No further information

No references
Analgesia (19/22)

No further information

References:

Relevant guidelines

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

Schmerztherapie bei Tumorerkrankungen http://www.krebsgesellschaft.de/download/l1_n_02.pdf
Diarrhea (20/22)

No further information

References:

Relevant Guidelines


**Constipation (21/22)**

*Further information:*

Constipation is not infrequently encountered during chemotherapy. Particularly around the time in autumn and winter, when indoor heating begins and air humidity is consequentially reduced. Sufficient fluid uptake should be 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 2005-2014:**
  - Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Rody / Scharl / Schneeweiss

- **Version 2015:**
  - Solomayer / Harbeck
Breast Cancer: Specific Situations

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

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

- Breast imaging & biopsy like in non-pregnant patients
- Staging: ultrasound, chest X-ray if indicated
- Surgery like in non-pregnant patients
- Sentinel node excision (technetium only)
  SNE 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)

Oxford / AGO LoE / GR

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<th>Level</th>
<th>Evidence</th>
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<td>+</td>
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<tr>
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<tr>
<td>Blue dye</td>
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</table>

* 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

Oxford / AGO
LoE / GR

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<td>MTX (e.g. CMF)</td>
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<td>Bisphosphonates</td>
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</table>

* Participation in register study recommended
Breast Cancer During Pregnancy*

- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity) 2b C ++
- Termination of pregnancy does not improve maternal outcome 3b C
- Delivery mode like in healthy women, avoid delivery ≤3 weeks from prior chemotherapy 4 C ++
- If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities 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
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
- Omit Radiotherapy after BCT in low risk with endocrine treatment**
- Trastuzumab

<table>
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<td>Endocrine treatment (endocrine resp.)</td>
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<td>A ++</td>
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<tr>
<td>Chemotherapy (standard regimens)</td>
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<td>&lt; 70 years</td>
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<tr>
<td>&gt; 70 years (especially N+, ER/PgR-)</td>
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<tr>
<td>Radiotherapy</td>
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<td>A +</td>
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<tr>
<td>Omit Radiotherapy after BCT in low risk with endocrine treatment**</td>
<td>2b</td>
<td>C +</td>
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</table>

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

*Study participation recommended
Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

- Reduced standard treatment
  - Options extrapolated from trials in elderly:
    - No breast surgery
      (consider endocrine options)
    - No axillary clearing (≥ 60 y, cN0, Rec pos)
    - No radiotherapy (≥ 65 y, pT1, pN0, Rec pos)
    - Hypofractionated radiotherapy
    - No chemotherapy if >70 years and negative risk-benefit analysis

Oxford / AGO LoE / GR

2b  C  ++
Male Breast Cancer: Diagnostic Work-Up and Loco-Regional Therapy

| Oxford / AGO LoE / GR | 4 | C | +
|-----------------------|---|---|---
|                       | 3b | C | +/- |
|                       | 2b | B | ++ |
| Diagnostic work-up as in women |     |   |   |
| Mammography          | 4  | C | ++* |
| Ultrasound           | 4  | C | * |
| Standard-surgery: Mastectomy |     |   |   |
| BCT my be an option (tumor breast relation) | 2b | B | + |
| Sentinel-node excision (SNE) |     |   |   |
| Radiotherapy as in women |     |   |   |
| (consider tumor breast relation!) | 4  | C | + |
| Genetic counselling if one additional relative affected (breast/ovarian cancer) | 2b | B | ++ |
| Screening for 2nd malignancies according to guidelines | GCP | ++ |

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

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

*Participation in register study recommended
Primary 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
- Staging
  - Skin punch biopsy (at least 2; detection rate < 75%) 2c B +
- Preoperative chemotherapy
  - Regimens as in non-inflammatory BC
    - Anthracycline and taxane-based 2b B ++
    - In HER2 + disease, addition of trastuzumab 2b B ++
    - In HER2 + disease, addition of trastuzumab and pertuzumab 2b B +
    - In Her2 - 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 2c B ++
- Postoperative systemic therapy as in non-inflammatory BC 4 C ++

Oxford / AGO LOE / GR

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<th>Grade</th>
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<td>4</td>
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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

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<th>Grade</th>
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<td>Breast MRI</td>
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<td>B ++</td>
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<tr>
<td>PET / PET-CT</td>
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<td>B +/-</td>
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<tr>
<td>Gene expression profiling (e.g. CupPrint™)</td>
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<td>B +/-</td>
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<td>ER, PgR, HER2</td>
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<td>D ++</td>
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<td>Axillary dissection</td>
<td>3a</td>
<td>C ++</td>
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<tr>
<td>Systemic treatment according N+ tumor</td>
<td>3a</td>
<td>C ++</td>
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<tr>
<td>Mastectomy if breast MRI is negative</td>
<td>3a</td>
<td>C -</td>
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<tr>
<td>Breast irradiation if breast MRI is negative</td>
<td>3b</td>
<td>C +/-</td>
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<td>Irradiation of regional lymph nodes according to breast cancer guidelines</td>
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### Paget’s Disease of the Breast

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

- Complete (wide) local excision or MRM
- SNE / Axillary dissection in cN0
- Staging
- Systemic adjuvant therapy (chemo, endocrine)
- Adjuvant radiotherapy
  - If T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy)
- Treatment of local recurrence
  - R0 resection
  - Radiotherapy, chemotherapy after R1 resection
- Distant metastases (very rare)

Oxford / AGO LOE / GR

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<tr>
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<tr>
<td>Distant metastases (very rare)</td>
<td>4</td>
<td>C</td>
<td>++</td>
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Sarcoma / Angiosarcoma of the Breast
(Note: very aggressive!)

Treatment of Primary Disease:
- Mammography, Sonography to determine extent of disease
- Preoperative MRI to determine extent of disease
- Diagnosis by core biopsy
- Diagnosis by FNB
- Staging
- Prognostic factors: size, grade, margins
- Surgery with wide clear margins
  - Breast-conserving therapy if feasible
- Axillary dissection if cN0
- Adjuvant chemotherapy, radiotherapy
  - Adjuvant chemotherapy (anthracycline-based), radiotherapy in case of high risk (grade II-III, size > 5 cm, R1)

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
- Trabectidin (after anthracycline/ ifosfamide failure in leiomyosarcoma)
Further information:

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

Screened data bases:
Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

Screened guidelines:

This chapter of rare diseases cannot deliver references for every statements separately but is providing them where possible.

No references
Breast cancer: Specific situations (3/18)

No further information

No references
Breast Cancer in Young Women ≤ 35 years (4/18)

Further information:

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

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

References:

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

**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

**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 (5/18)

Further information:

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

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

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

Another reason for the delayed diagnosis next to “simply not thinking about it” is the 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 (GBG registry):


Statement: Breast imaging & biopsy like in non-pregnant

1. Bock K et al., Rationale for a diagnostic chain in gestational breast tumor diagnosis. Arch Gynecol Obstet 2005

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 (6/18)

No further information

References:

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 (7/18)

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

6. Williams Obstetrics lecture book
**Pregnancy Associated Breast Cancer: Outcome (8/18)**

**Further information:**

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

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

**References:**

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


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 (9/18)

Further information:

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

References:

**Treatment for Fit Elderly Patients (10/18)**

*Further information:*

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

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

*References:*

*Statement: Treatment according to standard*


**Statement: Surgery similar to „younger“ age**


Statement: Endocrine treatment (endocrine resp.)

15. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381, 805–816

Statement: Chemotherapy in pts. < 70 years


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 surgery 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.

25. 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 (11/18)

Further information:

Frailty is a factor that is crucial in modern times for assessing older patients who are fit to undergo more invasive/aggressive management. The presence of multiple co-morbidities also affects outcome of surgery and/or adjuvant treatment for older breast cancer patients and can increase the risk of death from causes other than breast cancer. There thus may 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)

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

Statement: Hypofractionated radiotherapy


Statement: No chemotherapy > 70 years and negative risk benefit analysis

Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (12/18)

Further information:

General:
The median age of male breast cancer is around 10 years later than in female. Survival seems to be not inferior to that of women with breast cancer. Male breast cancer patients developed secondary malignancies in more than 20% of the patients. In general the level of evidence is low and most recommendations are linked to those of postmenopausal women.

Diagnostic:
In men 80-90% of malignant breast tumors are not detected by mammography or they are covered by a gynecomastia. Ultrasound seems more effective.

Surgery:
Wide excision in male breast cancer will almost always include resection of the nipple due to the small amount of breast tissue, and there is some evidence that this is not the most effective method of local control. To establish axillary status in clinically node-negative cases evidence is building up of the accuracy and low morbidity associated with sentinel-node biopsy in women. The technique has also been used in men with similarly encouraging results and sentinel node biopsy will probably become standard practice in the future for node-negative male breast cancer.

Genetic counselling:
Approximately 3-5% of female breast cancers are thought to result from autosomal dominant inheritance, particularly BRCA1 and BRCA2 mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in BRCA2 than BRCA1 families. In a southern Californian population, there were no BRCA1 mutations in 54 patients with male breast cancer, whereas there was a BRCA2 mutation in two (4%) patients. In 94 patients in the UK there were no germline BRCA1 mutations, but five (6%) patients had BRCA2 mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations with in the BRCA2 gene and risk of breast cancer.

Radiotherapy: Adjuvant radiotherapy has been delivered proportionally more frequently to men with breast cancer than to women, because the disease was more advanced locally in men and thought to be more aggressive. There is no evidence, however, that stage by stage the indications for radiotherapy should be different in men than in women. However,
retrospective studies that investigated the effects of radiotherapy in male breast cancer have not clearly shown a survival benefit.

References:

International registry:

General:

Statement: Diagnostic work up as in women

Statement: Mammography


Statement: Ultrasound

Statement: **Standard-surgery: Mastectomy –men**


Statement: **Sentinel-node excision (SNE)**


Statement: **Radiotherapy as in women (consider tumor breast relation!)**

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


**Statement: Screening for 2nd malignancies according guidelines**


**Statement: Systemic therapy**


Review articles

**Male Breast Cancer: Systemic Therapy (13/18)**

*Further information:*

Adjuvant chemotherapy: LoE: 4; References 1-4 (retrospective analysis, case series)
Adjuvant CMF chemotherapy was associated with an improvement in disease-free and overall survival. Only 50% of the patients (N=24) actually received the planned 12 cycles of CMF due to side effects.

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)
Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free survival and OS. Tamoxifen is well tolerated with the most common side effects being: Loss of libido (29%), weight gain (25%), heat flushes (21%), mood changes (21%), and depression (17%). The use of aromatase inhibitors has to be regarded as an experimental therapy at present. Due to the different physiological prerequisites for estrogen production in men and women, the effect of lowering serum estrogen levels in men has not yet been scientifically validated. Comparing adjuvant therapy with tamoxifen to aromatase inhibitors for 257 male breast cancer patients the overall survival was significantly better after treatment with tamoxifen.

Palliative endocrine therapy: LoE: 4; References 1-4 (retrospective analysis, case series)
In the metastatic setting there are data on achievement of stable disease being the maximum response to AI. Case reports do exist for anastrozol, letrozol and also fulvestrant.

Because of the low evidence level for the treatment of male breast cancer we believe that new studies should not exclude male patients. International registries should be participated in.

*References:*

*Statement: Adjuvant Chemotherapy*


**Statement Trastuzumab**


**Statement endocrine therapy**


*Statement palliative chemotherapy*

Primary Inflammatory Breast Cancer (IBC; cT4d) (14/18)

Further information:

There is little information on inflammatory breast cancer (IBC) alone. Most retrospective analysis focus on T4 carcinomas without separating T4d cancer. Primary IBC is probably a distinct biological entity compared to non IBC. Prospective randomised studies for the diagnosis and treatment of patients suffering from inflammatory breast cancer are still missing. The matter of current updates is aiming on the definition, including the confirmation of an invasive carcinoma as well as clinical signs of the skin affection $\geq 1/3$ of the breast involved (previous definition $> 2/3$ of the breast) [Dawood et al., 2011]. Biopsies of the skin should be acquired for diagnostic reasons [AGO 2c/B/+], with a detection rate of < 75%.

Because of that a multidisciplinary approach consisting of preoperative chemotherapy, mastectomy and postoperative radiotherapy and adjuvant treatment is necessary. In the NOAH trial patients with locally advanced HER2 positive breast cancer were randomized to chemotherapy and trastuzumab preoperatively followed by adjuvant trastuzumab after surgery or to preoperative chemotherapy alone. 27% of the patients had inflammatory disease. pCR rates were significantly higher with the combination of trastuzumab and chemotherapy. In addition trastuzumab significantly improved event-free survival both in the whole study group and in pts with inflammatory breast cancer.

The use of Trastuzumab as neoadjuvant treatment option for inflammatory breast cancer [AGO 2b/B/++] is further supported by the current data of the NOAH-study [Semiglazov et al., 2011].

References:

Statement: Staging


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


Axillary Metastasis in Carcinoma of Unknown Primary (CUP) (15/18)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in < or = 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 (16/18)**

*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:
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:

Statement: Core biopsy

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**


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 ≥ 2cm (BCT) or T ≥ 10cm (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


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:


Primary angiosarcoma (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent.

Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm. The imaging features of AS are non-specific in mammography and up to 33% are undetectable. On ultrasound examination, there is a heterogenous echogenicity with hyperechoic areas without acoustic shadowing. The most useful imaging technique to determine the extent of AS is breast MRI that shows hypervascular, heterogenous masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images.

Histologic grading is important for the assessment of prognosis with the 5-year recurrence free survival of 76% for low grade AS and 15% for high grade AS but reported survival data differ widely. The role of adjuvant radiotherapy and
chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with antracycline-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).

References:


Breast Cancer Follow-Up
Breast Cancer Follow-Up

- **Versions 2002–2014:**
  Bauerfeind / Bischoff / Blohmer / Böhme / Costa / Diel / Gerber / Hanf / Heinrich / Janni / Kaufmann / Kümmel / Lux / Möbus / Mundhenke / Oberhoff / Scharl / Solomayer / Thomssen

- **Version 2015:**
  Maass / Rody
Breast Cancer Follow-Up
Objectives I

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
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)
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
  2c B ++

- General counseling (genetics, HRT, prophylactic surgery, breast reconstruction)
  2c C +

Oxford / AGO
LoE / GR

4 C +
Breast Cancer Follow-Up
Objectives

Intervention with regard to co-morbidities and life-style risks in order to reduce negative effects on disease course

- **Treatment of type II-diabetes**
  (>25% undetected DM in postmenopausal BC patients)
  ++

- **Weight intervention**
  (if BMI <18.5 and >40)
  2a B +

- **Reduction of dietary intake** (at least 15 % calories from fat)
  in HR neg. breast cancer patients is associated with improved overall survival
  2b B +

- **Smoking**
  (bc related mortality 2 x and BC unrelated mortality 4 x elevated)
  2b B ++

- **Reduce alcohol consumption below 6 g/d**
  2b B +

- **Moderate sport intervention** when physical activity was reduced
  (rel. reduction of mortality up to 25%)
  1b A ++
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
### Follow-up Goals Reported by Health Professionals and Patients

<table>
<thead>
<tr>
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<th>Health professionals</th>
<th>Patients</th>
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<tbody>
<tr>
<td><strong>Often mentioned</strong></td>
<td>Early detection of recurrences and second tumors</td>
<td>Examination of the breast</td>
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<tr>
<td></td>
<td>Psychosocial support</td>
<td>Reassurance</td>
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<td>Guidance, information and referral</td>
<td>Guidance of patients, answering questions</td>
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<tr>
<td><strong>Occasionally</strong></td>
<td>Evaluation of treatment and treatment side effects</td>
<td>Evaluation of treatment and treatment side effects</td>
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<tr>
<td><strong>mentioned</strong></td>
<td>Early detection of metastases</td>
<td>Psychosocial support</td>
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<td>Clinical trials, building own database</td>
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Routine Follow-Up Examinations in Asymptomatic Patients

Tests:

- History (specific symptoms)  
  Oxford / AGO LoE / GR: 1a A ++

- Physical examination  
  1a B ++

- Breast self-examination  
  5 D +

- Mammography  
  1a A ++

- Sonography of the breast  
  2a B ++

- Routine MRI of the breast  
  3b B +/-

- MRI of the breast in case of inconclusive conventional imaging  
  3b B +

- Pelvic examination  
  5 D ++
Routine Follow-Up Examinations in Asymptomatic Patients

- **Routine biochemistry (incl. tumor markers)** 1a A -
- **Ultrasound of the liver** 1a A -
- **Bone scan** 1a A -
- **Chest X-ray** 1a A -
- **CT of chest, abdomen and pelvis** 2a D -
- **Detection of isolated / circulating tumor cells** 2a D -
- **PET** 2b B -
- **Whole body MRI** 2b B -

Oxford / AGO LoE / GR
Early Detection of Potentially Curable Events

Local recurrence & in-breast recurrence:

- Incidence 7–20%
  (depending on time of F/U)
- Breast self-examination 5 D +
- Physical examination, mammography & US 1a B ++
- Magnetic resonance imaging (MRI) 3b B +/-
Early Detection of Potentially Curable Events

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 -
Early Detection of Potentially Curable Events

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 (incl. LCIS/DCIS)

**Recommendations for asymptomatic pts.**
(modified ASCO guidelines 2012, NCCN 2.2011 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 4 5 &gt; 6</td>
<td>inv.: every 3 months  inv.: every 6 months  inv.: every 12 months  LCIS / DCIS: every 6-12 months  LCIS/DCIS: every 12 months</td>
</tr>
<tr>
<td>History, physical examination, counseling</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>inv.: every 3 months</td>
<td>inv.: every 6 months</td>
<td>inv.: every 12 months</td>
</tr>
<tr>
<td>Self-examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging modalities and biochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>indicated only by complaints, clinical findings or suspicion of recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammo- and sonography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inv.: BCT**</td>
<td>ipsilat.: every 12 months contralat.: every 12 months</td>
<td>on both sides: every 12 months</td>
</tr>
<tr>
<td>inv.: Mastectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>contralateral every 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCIS / DCIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>every 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Continued follow-up visits if still on adjuvant treatment

** First mammography 6-12 months after completion of breast-conserving radiotherapy
Breast Cancer Follow-up Duration. Breast Nurses.

- **Duration of follow-up**
  - until 5 yrs
  - until 10 yrs

- **Surveillance by specialized breast nurses**

Oxford / AGO
LoE / GR

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

*Studies recommended*
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 (2/17)

No further information

No references
Breast Cancer Follow-Up, Objectives I (3/17)

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

Breast Cancer Follow-Up, Objectives III (5/17)

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 (6/17)

No further information

References:

Statement: Early Detection

Statement: Psycho-social aspects


Statement: prophylactic surgery

Breast Cancer Follow-Up, Objectives (7/17)

No further information

References:

Statement: Early Detection

Statement: Psycho-social aspects


Follow-up Objectives - Reported by Patients (8/17)

No further information

References:

Follow-up Goals Reported by Health Professionals and Patients (9/17)

No further information

References:

Routine Follow-Up Examinations in Asymptomatic Patients (10/17)

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**

2. Geurts SM1, de Vegt F, Siesling S, Flobbe K, Aben KK, van der Heiden-van der Loo M, Verbeek AL, van Dijk JA, Tjan-Heijnen VC.
Routine Follow-Up Examinations in Asymptomatic Patients (11/17)

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 (12/17)

No further information

References:

Statement incidence


Statement breast self examination

Statement physical examination, mammography & US

Early Detection of Potentially Curable Events (13/17)

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 (14/17)

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 (incl. LCIS/DCIS) (15/17)

No further information

References:

Breast Cancer Follow-up - Duration. Breast Nurses. (16/17)

No further information

References:

Luminal-like, HER2-positive and Triple-negative Breast Cancer Patients (17/17)

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 2003–2014:**
  Audretsch / Bauerfeind / Costa / Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Hanf / Lisboa / Maass / Mundhenke / Rezai / Solomayer / Souchon / Thomssen

- **Version 2015:** Fersis / Harbeck
Loco-regional Recurrence
Incidence and Prognosis

<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>

Examinations before treatment:

- **Tissue Biopsy**
  - Oxford: 5, AGO: D, LoE: ++

- **Reassessment of ER, PR, HER2**
  - Oxford: 3b, AGO: B, LoE: ++

- **Complete re-staging**
  - Oxford: 5, AGO: D, LoE: ++
Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

**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)
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>

TNBC-subtype vs. other subtype

<table>
<thead>
<tr>
<th></th>
<th>ILRR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>1.88 (1.58-2.22)</td>
<td>2.12 (1.72-2.62)</td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

TNBC-subtype vs. HER2-subtype

<table>
<thead>
<tr>
<th></th>
<th>ILRR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.69 (0.53-0.91)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

ILRR: ipsilateral locoregional recurrence
DM: distant metastasis
TNBC: triple negative breast cancer
BCT: breast conserving therapy   ME: mastectomy
Risk Factors for Locoregional Recurrences after ME


IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence …:

...> 15% chest wall: age < 40; > 4 pos. nodes, 0-7 uninvolved nodes

...> 10% supraclavicular: > 4 pos. nodes

...> 5% axillary failure: age < 40; unknown tumor size, 0-7 uninvolved nodes

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/close margin
  (if ≥ 2 factors pos.)

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)
- Re-BCS with tumor-free margins
  ± flap reconstruction
  - Disadvantage for overall survival cannot be excluded
  - Impaired cosmetic result cannot be ruled out
  - Impaired local tumor control cannot be fully excluded
- Axillary intervention after prior AxDiss if cN0
- SNE after prior SNE if cN0*
- Palliative surgery in M1-situation
  (e.g. pain, ulceration, psychosocial)

*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 AGO LoE / GR: 2b A ++

- **Palliative situation: Resection of deep parts of the chest wall**
  - Oxford AGO LoE / GR: 5 D +/-

- **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**
  - Oxford AGO LoE / GR: 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 2b B ++
- Chemotherapy (consider neoadjuvant) 2b B +
- In case of HER2 positive disease
  Chemotherapy + HER2 targeted therapy 5 D +
CALOR Trial

n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection

5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy vs. 57% (44-67) without chemotherapy (hazard ratio 0.59 [95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).

Adjuvant chemotherapy was significantly more effective in ER negative disease (pinteraction=0.046).

Aebi et al. Lancet Oncol 2014
Locoregional Recurrence in Case R0
Resection not Likely - Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors 2b B ++
- Chemotherapy (pre- or postoperatively) 2b B ++
- HER2-targeted therapy in HER2-overexpressing tumors (with chemotherapy) 5 D ++
Ipsilateral Recurrence after BCT Radiotherapy

After Re-BCS

- Whole breast irradiation
  (in case adjuvant radiotherapy was not performed)
- Re-breast irradiation
  (Partial breast radiation, brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
  (14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)
## Chest-Wall Recurrence after Mastectomy

- **If no prior postmastectomy radiotherapy**
  - Curative situation: irradiation of the chest wall +/- regional lymph nodes
  - Re-irradiation (chest wall + hyperthermia)

## Axillary recurrence

**Irradiation of axilla after R0-surgery**

- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level of Evidence (LoE)</th>
<th>Grade (GR)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest-Wall Recurrence after Mastectomy</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Re-irradiation (chest wall + hyperthermia)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Axillary recurrence</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Adjuvant irradiation of the axilla</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Loco-Regional Recurrence Treatment Options in Non Curative Cases

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical chemotherapy (miltefosine)</td>
<td>3b</td>
<td>C</td>
</tr>
<tr>
<td>Concomitant radio-chemotherapy</td>
<td>3b</td>
<td>C</td>
</tr>
<tr>
<td>Hyperthermia (in centers listed on DKG website)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In combination with radiotherapy</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>In combination with chemotherapy</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Intra-arterial chemotherapy</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Electrochemotherapy</td>
<td>3b</td>
<td>C</td>
</tr>
</tbody>
</table>
**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


Statement: Grading (G3 vs. G1)


Statement: pT (> 2 vs. ≤ 2cm)


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 patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73(2):357-64, 2009

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**


**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

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)

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

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 2003–2014:**
  Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Loibl / Lück / von Minckwitz / Müller / Mundhenke / Nitz / Schneeweß / Schütz / Stickeler

- **Version 2015:**
  Liedtke / Möbus
Endocrine Therapy in Metastatic Breast Cancer

Indication

Oxford LoE: 1a  GR: A  AGO: ++

Endocrine therapy represents the first choice for metastatic breast cancer with positive (unknown) hormone receptor status.

- Exception: acute life threatening disease
- Cave: HR might change during the course of the disease. Histology of recurrent site should be obtained whenever possible
Comparison ER/PR and HER2 Metastasis vs. Primary Tumor

Metaanalysis based on 48 (mostly retrospective) analyses:

Pooled discordance proportions were
- 20% (95%CI 16-35%) for ER
- 33% (95%CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Pooled proportions of tumours shifting from positive to negative and negative to positive were
- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2
Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer

- GnRHa + tamoxifen (vs. OFS or Tam)
  - Oxford / AGO LoE / GR: 1a A ++
- Ovarian function suppression (OFS)
  - Oxford / AGO LoE / GR: 2b B +
- Tamoxifen
  - Oxford / AGO LoE / GR: 2b B +
- GnRHa + AI (first or second line)
  - Oxford / AGO LoE / GR: 2b B +
- GnRHa + Fulvestrant
  - Oxford / AGO LoE / GR: 4 C +/-
- Aromatase inhibitors without OFS
  - Oxford / AGO LoE / GR: 3 D - -
Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer

Treatment options for postmenopausal patients pretreated with adjuvant tamoxifen or without adjuvant endocrine therapy

- **Aromatase inhibitors (3rd gen) (> non-AI*)**  
  1a A ++

- **Tamoxifen (vs. no therapy)**  
  1a A ++

- **Fulvestrant 500 mg**  
  1b B ++

- **Fulvestrant 250 mg (= AI)**  
  2b B +

- **MPA/MA (< AI)**  
  1a A +/-

- **Fulvestrant 250 mg + AI (vs. AI)**  
  1b B +/-

- **Letrozol + Palbociclib (vs. Letrozol)**  
  2b B +/-

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus + exemestane are indicated after AI treatment, a non-steroidal AI should be preferred in first line.*
Endocrine Therapy  in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer  (after Adjuvant Tamoxifen or no Prior Endocrine Treatment)

<table>
<thead>
<tr>
<th>Treatment sequence</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line:</strong> aromatase inhibitors (3rd gen)*</td>
<td>1a A ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg + anastrozole</td>
<td>2b C +/-</td>
</tr>
<tr>
<td><strong>2nd line:</strong> fulvestrant</td>
<td>1b B</td>
</tr>
<tr>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td>fulvestrant 250 mg</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>exemestane + everolimus</td>
<td>1b A ++</td>
</tr>
<tr>
<td>aromatase inhibitor**</td>
<td>2b B +</td>
</tr>
<tr>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td><strong>Further lines:</strong> tamoxifen</td>
<td>3b C +</td>
</tr>
<tr>
<td>MPA/MA</td>
<td>4 D +/-</td>
</tr>
<tr>
<td>estradiol 6 mg daily</td>
<td>3b C +/-</td>
</tr>
<tr>
<td>repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>

* To date, there is no evidence for superiority of a single aromatase inhibitor. ** steroidal or non-steroidal depending on previous AI
Therapy Algorithm After Adjuvant Tamoxifen

Non-steroidal AI 3rd generation

Exemestane + everolimus

Fulvestrant 500 mg

Fulvestrant 500 mg

Tamoxifen

Fulvestrant 500 mg

Exemestane + everolimus

Tamoxifen
# Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer after Adjuvant AI

## Treatment sequence

<table>
<thead>
<tr>
<th>Line</th>
<th>Treatment Options</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tamoxifen</td>
<td>2b B ++</td>
</tr>
<tr>
<td></td>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td></td>
<td>exemestane + everolimus* (relapse within 12 mths)</td>
<td>1b A ++</td>
</tr>
<tr>
<td></td>
<td>steroidal after non-steroidal AI</td>
<td>2b B +</td>
</tr>
<tr>
<td></td>
<td>non-steroidal after steroidal AI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>2nd line:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fulvestrant 500 mg</td>
<td>1b B ++</td>
</tr>
<tr>
<td></td>
<td>exemestane + everolimus*</td>
<td>1b A ++</td>
</tr>
<tr>
<td></td>
<td>tamoxifen (if previously not given)</td>
<td>5 D +</td>
</tr>
<tr>
<td></td>
<td>tamoxifen + everolimus</td>
<td>2b B +</td>
</tr>
<tr>
<td>Further lines:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPA/MA</td>
<td>4 C +/-</td>
</tr>
<tr>
<td></td>
<td>repeat prior treatments</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>

*After pretreatment with at least a non-steroidal AI in the metastatic and/or adjuvant setting
**trial participation
Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab

- Maintenance Bevacizumab plus endocrine therapy after remission with chemotherapy and Bevacizumab  
  2ba  B  +

- Bevacizumab plus endocrine treatment as first line therapy for advanced disease  
  1ba  B  -
Therapy Algorithm After Adjuvant AI

**Short treatment free interval ≤12 months**
- **Exemestane + everolimus**
  - **Fulvestrant 500 mg**
  - **Tamoxifen**

**Long treatment free interval >12 months**
- **Fulvestrant 500 mg**
- **Tamoxifen**
- **Exemestane + everolimus**
  - **Tamoxifen**
  - **Fulvestrant 500 mg**
HER2 Positive and HR-Positive Metastatic Breast Cancer
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients

- Anastrozole and trastuzumab
- Letrozole and trastuzumab
- Letrozole and lapatinib
- Fulvestrant and lapatinib

<table>
<thead>
<tr>
<th>Therapy Combination</th>
<th>Oxford/AGO LoE</th>
<th>Grade</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole and trastuzumab</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Letrozole and trastuzumab</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Letrozole and lapatinib</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Fulvestrant and lapatinib</td>
<td>1b&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

Poor efficacy of endocrine therapy alone. Consider chemotherapy + anti-HER2-therapy!
## Combination of Endocrine Treatment with Anti-HER2-Treatment

<table>
<thead>
<tr>
<th>Treatment (no. of pats)</th>
<th>PFS (mo)</th>
<th>Response (CBR)</th>
<th>OS (mo)</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 central 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>n.r.</td>
</tr>
<tr>
<td>Lapatinib + letrozole vs. letrozole (n=219/1286)</td>
<td>8.2 vs. 3.0</td>
<td>48% vs. 29%</td>
<td>33.3 vs. 32.3 mo</td>
</tr>
<tr>
<td>Lapatinib + fulvestrant vs. fulvestrant (n=267/324)</td>
<td>4.1 vs. 3.8 (HER2-) 5.9 vs. 3.3 (HER2+)</td>
<td>38 vs. 17%</td>
<td>30 vs. 26.4 mo (all)</td>
</tr>
</tbody>
</table>
Concomitant or Sequential Endocrine-Cytostatic Treatment

- Concomitant endocrine-cytotoxic treatment
  - Increases response rates without prolongation of progression free interval or overall survival
  - Increases toxicity

- Maintenance endocrine therapy after chemotherapy induced response
  - Increases progression free interval

Oxford / AGO LoE / GR

1b A - -

3 C ++
Endocrine Therapy of Metastatic Breast Cancer (2/15)

Further information:

Screened data bases Pubmed, ASCO, San Antonio, EBCC, ESMO

No references
Endocrine Therapy in Metastatic Breast Cancer – Indication (3/15)

Further information and references:

Endocrine therapy as the first choice in hormone receptor positive breast cancer

Endocrine therapy remains the most important approach to the treatment of hormone-sensitive non-life-threatening metastatic breast cancer. This systemic therapy has the advantage of combining efficacy, minimal toxicity, and good quality of life. Endocrine therapy use in clinical practice is based on a positive estrogen receptor (ER) and/or progesterone receptor status of the primary tumour or, if at all possible, of an easily accessible metastasis. This type of therapy is usually the first choice when the risk of rapid disease progression is low, i.e. if there is no life-threatening disease. The selection of the most appropriate endocrine therapy takes into account the menopausal status of the patient, the type of adjuvant endocrine therapy received, and past medical history of thrombolic disease. HER-2-positive metastatic breast cancer is less responsive to any type of endocrine treatment. This effect holds in the subgroup of patients with positive or unknown steroid receptors

Response to endocrine therapy by hormone receptor status

A Cochrane Data Base Meta-Analysis was performed in 2003 on whether chemotherapy alone versus endocrine therapy alone for metastatic breast cancer is more favorable. The primary analysis of overall effect using hazard ratios derived from published survival curves involved six trials (692 women). There was no significant difference seen (HR=0.94, 95%CI 0.79-1.12, p=0.5). A test for heterogeneity was p=0.1. A pooled estimate of reported response rates in eight trials involving 817 women shows a significant advantage for chemotherapy over endocrine therapy with RR=1.25 (1.01-1.54, p=0.04). However the two largest trials showed trends in opposite directions, and a test for heterogeneity was p=0.0018. There was little information available on toxicity and quality of life. Six of the seven fully published trials commented on increased toxicity with chemotherapy, mentioning nausea, vomiting and alopecia. Three of the seven mentioned aspects of quality of life, with differing results. Only one trial formally measured quality of life, concluding that it was better with chemotherapy.
The Reviewers concluded that in women with metastatic breast cancer and where hormone receptors are present, a policy of treating first with endocrine therapy rather than chemotherapy is recommended except in the presence of rapidly progressive disease.

References:


Changes in receptor profiles

Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting.

Several retrospective studies have evaluated this biological phenomenon with divergent results.

A recently published retrospective study (Broom et al., 2009) evaluated data from 100 patients for whom tissue from primary and metastatic sites was available. Estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu status in the primary and metastasis were compared. The discordance rate for ER was 17.7% (2-sided \( p=0.0039 \)) with 9.7% of tumors changing from ER-positive to ER-negative and 8.0% changing from ER-negative to ER-positive. The discordance rate for PR was 37.3% (2-sided \( p<0.0001 \)), with all of these tumors changing from PR-positive to PR-negative. No significant discordance for Her-2/neu was found. This study suggested that significant discordance exists for hormone receptor status between primary and metastatic breast cancer samples. Loss of PR was particularly frequent.

One prospective study, BRITS (Breast Recurrence In Tissue Study), investigated 137 matched primary and recurrent breast cancer tissue samples. The recurrent biopsy was excisional tissue in 100 (73%) and core biopsy in 37 (27%). Central laboratory analysis of the original primary was ER positive in 109 (79.6%), PR positive in 85 (62.0%) and HER2 positive in 14 (10.2%); the recurrent disease was ER positive in 101 (73.7%), PR positive in 75 (54.7%) and HER2 positive in 16 (11.7%).
A switch in receptor status, in either direction, was identified for ER in 14 patients (10.2%; p=0.983 Wilcoxon sign rank test), PR in 34 (24.8%; p=0.003 Wilcoxon sign rank test) and HER2 in 4 (2.9%; p=0.074 Wilcoxon sign rank test). In the judgement of the investigators the switch led to a change in the subsequent treatment in 24 patients (17.5%). This study demonstrated that the management of locally recurrent or metastatic breast cancer should include tissue sampling, since switches of ER, PR or HER2 status in the breast cancer recurrence may change the planned treatment for one in six patients (Thompson 2009).
Additionally there is further evidence for a prognostic impact of receptor profile changes in metastatic breast cancer: In a retrospective analysis, patients with tumors that changed from ER positive primary to negative metastasis experienced a significantly shorter median survival than patients with unchanged receptor profiles, while changes in PR status were not associated with a change in survival. Therefore, optimal metastatic treatment cannot be determined solely on primary ER and PR analyses (Lower et al. 2005).

References:

5. Li BD, Byskosh A, Molteni A, Duda RB Estrogen and progesterone receptor concordance between primary and recurrent breast cancer.
Further information:

Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting. Several retrospective studies have evaluated this biological phenomenon with divergent results.

References:

Endocrine Therapy in Premenopausal Patients with HER2 Negative Metastatic Breast Cancer (5/15)

Further information and references:

GnRHa + tamoxifen

The combination of GnRH + tamoxifen represents the first choice as endocrine first line therapy of hormone receptor positive premenopausal breast cancer. Due to the results of one randomized trial and a metaanalysis of additional 4 trials in a three-arm, randomized, prospective trial a total of 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with buserelin, tamoxifen, or both. The median follow-up was 7.3 years. Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by objective response rate (48%, 34%, and 28% respectively; P = .11 [chi(2) test]), median progression-free survival (9.7 months, 6.3 months, and 5.6 months; P = .03), and overall survival (3.7 years, 2.5 years, and 2.9 years; P = .01). Actuarial 5-year survival percentages were 34.2%, 14.9%, and 18.4%, respectively. No differences in antitumor effects were observed between single-agent treatment groups (Klijn et al. 2000). For patients with solitary bone metastasis a prospective multicenter study on 318 patients revealed even a survival benefit besides a significant improvement of pregression free survival (Jonat et al 1995).

The metaanalysis (Klijn et al. 2001) confirmed the above findings in four clinical trials randomizing a total of 506 premenopausal women with advanced breast cancer to LHRH agonist alone or to the combined treatment of LHRH agonist plus tamoxifen. With a median follow-up of 6.8 years, there was a significant survival benefit (P = .02; hazards ratio [HR] = 0.78) and progression-free survival benefit ( P = .0003; HR = 0.70) in favor of the combined treatment. The overall response rate was significantly higher on combined endocrine treatment ( P = .03; odds ratio = 0.67).

References:


**Ovarian function suppression, tamoxifen**

A further option in the treatment of metastasized premenopausal hormone receptor positive breast cancer is ovarian ablation. Oophorectomy and GnRHa have been demonstrated to be equally efficacious in the metastatic setting. Taylor et al. evaluated these two methods for premenopausal patients with ER-positive, PR-positive, and unknown hormone status metastatic breast cancer. 136 patients were randomly assigned to either bilateral oophorectomy (n = 67) or goserelin (n = 69). The overall response rate was 31% for those in the goserelin group versus 27% in the oophorectomy group. The complete response (CR) rate for the two arms was 14 and 10%, respectively. The response rates between the two arms were not statistically significant.

An additional randomized, nonblinded trial compared oophorectomy and radiation ablation for metastatic breast cancer, 97 patients were treated with oophorectomy, and 61 had ovarian ablation by radiation. In the oophorectomy arm, 30% had a response (CR + partial response), and 18% had stable disease. In the radiation arm, 21% had a response (CR + partial response), and 15% had stable disease. These differences were not statistically significant (Lees et al. 1980).

Tamoxifen is well established as an alternative to ovarian suppression as first-line treatment for hormone receptor-positive breast cancer in the metastatic setting, especially in case of contraindications against a combination therapy with GnRHa (Oborne 1998). Several studies were reported over the last decade (Ingle et al. 1986, Buchanan et al. 1986, Sawka et al. 1997).

A meta-analysis of randomized trials comparing tamoxifen to ovarian ablation carried out either by surgery or irradiation as first-line hormonal therapy for pre-menopausal women with metastatic breast cancer enrolled 220 patients in four trials.
There was no difference in overall response rate between tamoxifen and oophorectomy across the four trials \((p = 0.94, \text{Mantel-Haenszel test})\). The odds reduction for progression was 14\% +/- 12\% and for mortality 6\% +/- 13\% in favour of tamoxifen, which was not statistically significant \((p = 0.32 \text{ and } 0.72, \text{respectively})\). Although the design of all four studies included a cross-over to the other therapy, only 54/111 patients receiving ovarian ablation and 34/109 patients receiving tamoxifen as primary therapy actually crossed over to the other arm at the time of disease progression. The efficacy of tamoxifen appears to be similar to that of ovarian ablation by surgery or irradiation as first-line therapy for premenopausal, ER positive metastatic breast cancer (Crump et al. 1997).

References:

Even if the evidence is rather limited, aromatase inhibitors can be an option in the treatment of metastatic premenopausal breast cancer. Majorly based on a Phase II trial by Forward et al. the combination of GnRHα plus aromatase inhibitors is a second line option after GnRHα + tamoxifen treatment failure. A total of 16 premenopausal women with metastatic breast cancer (N=13) or locally advanced primary breast cancer (N=3) were treated with a combination of a gonadotropin-releasing hormone agonist goserelin, and a selective aromatase inhibitor anastrozole. All had previously been treated with goserelin and tamoxifen. In all, 12 patients (75%) achieved objective response or durable stable disease at 6 months, with a median duration of remission of 17+ months (range 6-47 months). Four patients still have clinical benefit. Introduction of goserelin and tamoxifen resulted in an 89% reduction in mean oestradiol levels (pretreatment vs 6 months=224 vs 24 pmol l(-1)) (P<0.0001). Substitution of tamoxifen by anastrozole on progression resulted in a further 76% fall (to 6 pmol l(-1) at 3 months) (P<0.0001) (Forward et al. 2004). Additionally there is evidence for GnRHα+ aromatase inhibitors as first line treatment in premenopausal patients. Besides a case study of 3 patients (El-Saghir et al. 2006), a small randomized trail compared GnRHα + anastrozol vs. GnRHα+ tamoxifen in 119 peri/premenopausal women with hormone dependent metastatic breast cancer (Milla-Santos et al.2002). In comparison to GnRHα+tamoxifen the study combination showed higher response rates (80% vs. 53%, P=0.023), improved clinical benefit rates (P=0.05) as well as prolonged overall survival (18.9 vs. 14.3 months). However, since this study is very small, additional body of evidence is needed before general treatment recommendations can be made. Recently a cohort of 32 patients with metastatic disease were treated with GnRHα+anastrozol: One participant (3.1%) experienced a complete response, 11 (34.4%) experienced partial response, and 11 (34.4%) experienced stable disease for 6 months or longer for a clinical benefit rate of 71.9%. Median time to progression was 8.3 months (range, 2.1 to 63+) and median survival was not been reached (range, 11.1 to 63+).

References:


**GnRH plus Fulvestrant**

GnRH analogues can be combined with fulvestrant. This combination can be an alternative approach in selected cases e.g. if there is a contraindication for tamoxifen or ARH.

**References:**

Endocrine Therapy in Postmenopausal Patients with HER2 Negative Metastatic Breast Cancer (6/15)

Further information:

In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy. 3rd Generation aromatase agents should be the first endocrine treatment choice in patients with distant metastases of hormone responsive breast cancer and no adjuvant aromatase inhibitor treatment. This is demonstrated in numerous clinical trials and confirmed in a meta-analysis updated in 2009 (see references).

The clinical benefit of tamoxifen for treatment of metastatic breast cancer is shown in numerous trials and tamoxifen remains a major treatment option in the metastatic setting despite the superiority of aromatase inhibitors for first line treatment.

Fulvestrant in the approved dose of 250mg every four weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of MBC.

Despite convincing preclinical data supporting the combined therapy strategy of fulvestrant plus an aromatase inhibitors, there is overall conflicting evidence regarding efficacy in patients. While evidence from two prospective clinical trials (i.e. FACT and SoFEA) did not demonstrate any advantage by adding fulvestrant to anastrozole another trial showed that the combination of anastrozole and fulvestrant was superior to anastrozole alone or sequential anastrozole and fulvestrant. Therefore, combined use of these agents cannot be recommended.

MPA/MA are options as sequential therapies after other endocrine therapies have been used. However, they seem to be inferior to AI.

Trials comparing aromatase inhibitors for their efficacy have not delivered conclusive results, although one study stated that response with anastrozole was higher compared with letrozole. However, this was not the primary end point of this trial (see references “comparison of different AI”)

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 2003 39

5. Bonneterre, J, Buzdar, A, Nabholz, JA, Robertson, JFR, Thuerlimann, B, von Euler, M, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


“Fulvestrant is equivalent to AI (or tamoxifen) in the first line endocrine treatment of metastatic breast cancer”

2. Howell, A, Robertson, JFR, Quaresma Albano, J, Ascgermannova, 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
3. 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 250 mg vs. 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 anastrozole**


Letrozole and Palbociclib

Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients after Adjuvant Tamoxifen or no prior Endocrine Treatment (7/15)

Further information:

Evidence suggests that switching therapy from non-steroidal to a steroidal AI is as effective as fulvestrant in its approved dose of 250mg/q4 weeks (study “EFFECT”). It therefore seems as likely that a switch from steroidal to non steroidal AI is effective and may therefore represent a therapeutic option.

In women with advanced breast cancer and acquired resistance to aromatase inhibitors, a daily dose of 6 mg of estradiol provided a similar clinical benefit rate of 28% as 30 mg, with fewer serious adverse events.

References:

Estradiol


Fulvestrant and anastrozole

Exemestane and everolimus


Tamoxifen and everolimus

Therapy Algorithm After Adjuvant Tamoxifen (8/15)

No further information

No references
**Further information:**

For patients with progression or relapse after a short treatment free interval after the adjuvant use of an AI (in studies usually considered as one year or less), the same considerations as for second line treatment after AI use should be applied. In a randomised Phase-II-study the addition of palbociclib to letrozole significantly improved progression-free survival in women with advanced oestrogen receptor-positive and HER2-negative breast cancer. A phase 3 trial is currently underway.

**References:**

**Endocrine Therapy in Postmenopausal HER2 Negative Metastatic Breast Cancer Patients in combination with Bevacizumab (10/15)**

*Further information:*

For patients with HR-positive advanced breast cancer on first-line therapy with bevacizumab in combination with chemotherapy who discontinue chemotherapy without evidence of progression, continuation of bevacizumab therapy in combination with endocrine therapy is recommended until disease progression or toxicity. In the LEA study adding bevacizumab to first-line endocrine therapy with letrozole or fulvestrant failed to demonstrate significant increases in progression-free survival in postmenopausal women with advanced human epidermal growth-factor receptor 2 (HER2)-negative and hormone-receptor-positive (HR+) breast cancer.

*References:*


Therapy Algorithm After Adjuvant AI (11/15)

No further information

No references
Endocrine Therapy in Postmenopausal HER2 Positive Metastatic Breast Cancer Patients (13/15)

Further information:

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aromatase inhibitor treatment is able to enhance the efficacy over endocrine treatment alone. However, given the relative short progression free interval in the phase 3 trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients. One phase III trial comparing fulvestrant + placebo vs. Fulvestrant + lapatinib could not demonstrate an improved PFS or OS in 324 patients pretreated with an AI. For further information on trials combining endocrine treatment with anti-HER2 therapy, see following slide.

References:


Combination of Endocrine Treatment with Anti-HER2-Treatment (14/15)

**Further information:**

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aromatase inhibitor treatment is able to enhance the efficacy over endocrine treatment alone. However, given the relative short progression free interval in the phase 3 trials compared to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients. One phase III trial comparing fulvestrant + placebo vs. Fulvestrant + lapatinib could not demonstrate an improved PFS or OS in 324 patients pretreated with an AI.

For further information on trials combining enocrine treatment with anti-HER2 therapy, see following slide.

**References:**


Concomitant or Sequential Endocrine-Cytostatic Treatment (15/15)

Further information:

Concomitant endocrine cytostatic therapy can not be recommended because it induces an increase in toxicity and does not induce a prolongation of disease free interval or overall survival despite the increase of response rates. Thus, endocrine – cytostatic therapy should be performed as sequential treatment modality. Endocrine mainenance therapy after chemotherapy induced response might be considered, even if the evidence is quite small and not homogeneous, since only relatively little side effects are observed with this sequential treatment option.

References:

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 2003–2014:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Möbus / Rody / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thomssen

- **Version 2015:**
  von Minckwitz / Müller
Disease-Free and Overall Survival in Metastatic Breast Cancer

- 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

Oxford / AGO
LoE / GR

2a
2a
1b
1b
## Treatment of Metastatic Breast Cancer

### Predictive Factors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine therapy</td>
<td>ER / PR</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>(primary tumor, metastasis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>previous response</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>previous response</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Anti-HER2-drugs</td>
<td>HER2</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>(primary tumor, better metastasis)</td>
<td></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
  - LoE: 2b
  - AGO: B
  - Oxford: +

- Treatment until best response
  - LoE: 2b
  - AGO: B
  - Oxford: +/-

- Change to alternative regimen before progression
  - LoE: 2b
  - AGO: B
  - Oxford: +/-

- Stop therapy in case of
  - LoE: 1c
  - AGO: A
  - Oxford: ++

  - Progression
  - Non tolerable toxicity
Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends on:

- ER / PR, HER2; combination with biologicals
- Previous treatments (and their toxicities)
- Disease-free interval after end of adjuvant treatment
- Aggressiveness of disease and localization of metastases
- Estimated life expectancy
- Co-morbidities (including organ dysfunctions)
- Patients preference and expectations
## MBC HER2-negative/HR-positive Cytotoxic 1st-Line Therapy*

### Monotherapy:

- Paclitaxel (q1w), Docetaxel (q3w)  
  - Oxford / AGO LoE / GR: 1b A ++
- Doxorubicin, epirubicin, mitoxantrone (A)  
  - Peg. liposomal doxorubicin (A<sub>lip</sub>)  
  - Oxford / AGO LoE / GR: 1b A ++
- Vinorelbine  
  - Oxford / AGO LoE / GR: 3b B +
- Capecitabine  
  - Oxford / AGO LoE / GR: 2b B +
- Nab-paclitaxel  
  - Oxford / AGO LoE / GR: 2b B +

### Polychemotherapy:

- A + T  
  - Oxford / AGO LoE / GR: 1b A ++
- T + gemcitabine after adj. A  
  - Oxford / AGO LoE / GR: 2b B ++
- A + C or A<sub>lip</sub> + C  
  - Oxford / AGO LoE / GR: 1b B ++
- Paclitaxel + capecitabine  
  - Oxford / AGO LoE / GR: 2b A +
- Docetaxel + capecitabine after adj. A  
  - Oxford / AGO LoE / GR: 1b A +

*In ER pos. disease only if endocrine therapy is not or not anymore indicated
MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel q1w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Docetaxel q3w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Docetaxel + Peg-liposomal Doxo</td>
<td>1b</td>
<td>B</td>
<td>+/−</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

- Experimental therapies within studies
- Capecitabine
- Eribulin
- Vinorelbine
- (Peg)-liposomal Doxorubicin
- Gemcitabine + Cisplatin / Carboplatin
- Gemcitabine + Capecitabine
- Gemcitabine + Vinorelbine*

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LoE</th>
<th>Grade</th>
<th>Rating</th>
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</thead>
<tbody>
<tr>
<td>Experimental therapies within studies</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</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>Vinorelbine</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>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine*</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

*Cave neutropenia / therapeutic index!
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

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Efficacy</th>
<th>Evidence Level</th>
<th>Grade</th>
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<tbody>
<tr>
<td>++</td>
<td>++</td>
<td></td>
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</tr>
<tr>
<td>+</td>
<td>B</td>
<td>1b</td>
<td>a</td>
</tr>
<tr>
<td>+</td>
<td>B</td>
<td>1b</td>
<td>a</td>
</tr>
</tbody>
</table>
|+|B|1b|a|A|+
|+|B|2b|

www.ago-online.de
Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

1st line in combination with:
- Paclitaxel (q1w)
- Capecitabine
- Anthracyclines
- Nab-Pac
- Docetaxel (q3w)

Cap+Bev as maintenance after Doc+Bev

2nd line as treatment through multiple lines

2nd line in combination with:
- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

Oxford / AGO LoE / GR

1b  B  +
2b  B  +/-
1b  B  +/
1b  B  +/-
First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

- Docetaxel + trastuzumab + pertuzumab
- (nab)Paclitaxel + trastuzumab + pertuzumab
- T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)
- 1st line chemotherapy* + trastuzumab
- Trastuzumab mono
- Taxanes + lapatinib
- Taxanes + trastuzumab + everolimus
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

Oxford / AGO LoE / GR

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

*Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel

**see chapter Endocrine +/- targeted
### 2nd line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>Oxford / AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-DM 1</strong></td>
<td>1b A ++</td>
<td></td>
</tr>
<tr>
<td><strong>TBP: 2nd line chemotherapy + trastuzumab</strong></td>
<td>2b D +</td>
<td></td>
</tr>
<tr>
<td><strong>Capecitabine + lapatinib</strong></td>
<td>1b B +</td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab + lapatinib (HR neg. disease)</strong></td>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td><strong>Taxane + trastuzumab + pertuzumab</strong></td>
<td>5 D +</td>
<td>+/-</td>
</tr>
<tr>
<td><em><em>Any other 2nd line chemotherapy</em> + trastuzumab + pertuzumab</em>*</td>
<td>5 D +/-</td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab + aromatase inhibitors (if ER+)</strong></td>
<td>3b B +</td>
<td></td>
</tr>
<tr>
<td><strong>Lapatinib + aromatase inhibitors (if ER+)</strong></td>
<td>3b B +</td>
<td></td>
</tr>
</tbody>
</table>

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

---

**Guidelines Breast Version 2015.1**
Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

Pretreatment with Trastuzumab

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

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen

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 1\textsuperscript{st} line
- Capecitabine in > 2\textsuperscript{nd} line
- AI in ER positive disease

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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>2b</th>
<th>B</th>
<th>+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>AI in ER positive</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>
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;…)

Oxford / AGO LoE / GR

5  D  --

4  C  +/-

++
Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/18)

Further information and 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 Metastastic Breast Cancer (3/18)**

*No further information*

**References:**

Increase


More adjuvant..

Multiple lines

Treatment of Metastatic Breast Cancer - Predictive Factors (4/18)

No further information

References:

CTC monitoring


(Hilner et al. 2003 JCO)
Cytotoxic Therapy Goals (5/18)

Further information and references:

(Sledge et al, 2003).
(S Carrick et al, The Cochrane Database of Systematic Reviews 2005)

2013

Combination vs single agent


Docetaxel alone or in combination
Meta-analysis; MBC
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.

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 (6/18)

No further information

References:

Cytotoxic Therapy Duration (7/18)

Further information:

Consent
Treatment until progression 6++, 18+, 2+-, 1-
Treatment until best response 1++, 3+, 23+-, 1-
Change to alternative regimen before progression 1++, 0+, 25+-, 5-

References:

Change to alternative regimen before progression:

Treatment until progression
3. Park et al. JCO 2013
**Chemotherapy for MBC – General Considerations: Drug Selection (8/18)**

*Further information:*

The selection of the drugs and drug combinations should take into account patients expectations, general health conditions, aggressiveness of the disease, localisation of metastases and previous therapies.

*References:*

2013
Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better


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 (9/18)

Further information and 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. Doxorubicin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL. Cassier et al., Breast Cancer Research and Treatment (electronic publication 2007).

2013

Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Nab-Paclitaxel
1st line MBC, rand Phase II (n=302)
Treatment with nab-paclitaxel 150 mg/m(2) qw 3/4 resulted in a median overall survival (OS) of 33.8 months compared with 22.2, 27.7, and 26.6 months for nab-paclitaxel 100 mg/m(2) qw 3/4, nab-paclitaxel 300 mg/m(2) q3w, and docetaxel, respectively (overall P = .047).
A trend toward a longer OS was noted in the 150 mg/m(2)nab-paclitaxel arm versus docetaxel arm (hazard ratio, 0.688). Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms compared with docetaxel.


Ixabepilone + capecitabine vs capecitabine alone in 1st line MBC


Results: In 293 patients, ixabepilone plus capecitabine, as compared to capecitabine alone, increased PFS (median: 5.6 months vs. 2.8 months; hazard ratio, 0.58; p < 0.0001), ORR (46% vs. 24%) and OS (median: 15.1 months vs. 12.5 months; hazard ratio, 0.84; p = 0.208). Major toxicities of this regimen included neuropathy, neutropenia and hand-foot syndrome, but were manageable.
Metaanalyses
Docetaxel alone or in combination
Metaanalysis; MBC
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.


MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (10/18)

Further information and references:

Consent:

Eribulin: 5++, 21+, 4+/-


Suggested after anthracyclines (in alphabetical order): Capecitabine, Docetaxel, study-integrated experimental therapies, Gemcitabine, Pegliposomal Doxorubicin, Paclitaxel and Vinorelbine.

As monotherapy after anthracyclin-pretreatment only Docetaxel improved OAS as compared to a standard treatment arm in a prospective randomized trial in metastatic breast cancer (Nabholtz et al, 1999).

A Cochrane-metaanalysis of taxane treatment in metastatic breast cancer (Ghersi et al, 2003) shows a significant survival advantage as compared to non-taxane-based therapies. There was no significant difference in QoL or treatment related deaths. Final analysis of further end points was difficult due to significant heterogeneity of the single studies.

Indirect and direct comparisons of docetaxel and paclitaxel show a trend towards higher efficacy of docetaxel (Ghersi et al, 2003; Ravdin et al, 2003). Due to different toxicity profiles of each substance individual indication is needed.

Docetaxel in Combination with Pegliposomal Doxorubicin was superior to docetaxel alone in a randomised phase III trial by Sparano et al. It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantage from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.

2013
Nab-Paclitaxel
MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (11/18)

Further information and references:


Nab Paclitaxel (100-150mg/m² d1,8,15,q28) has been tested in different populations. Not all pts received an anthracycline and a taxane. It seems that a weekly dosing is superior to a 3 weekly dosing in terms of efficacy and side effects. Suggested after anthracycline and taxane treatment (alphabetical order): capecitabine, study-integrated experimental therapies, pegliposomal doxorubicin and vinorelbin. Studies with more than 100 patients showed overall remissions of 9% and 20% using vinorelbine and pegylated liposomal doxorubicin vs. capecitabine, respectively and a median survival of 9 months and 13 months. Ixabepilone/Capecitabine vs. Capecitabine after anthracycline and taxane treatment in metastatic breast cancer is a phase III randomised trial showing a significant improvement in PFS for the combination with a higher toxicity especially in neurotoxicity. Ixabepilone is not licensed in Germany; Thomas et al., JCO 25:5210-7 (2007) Gemcitabine/vinorelbine vs. vinorelbine after anthracycline/taxane treatment in metastatic breast cancer; Martin et al., Lancet Oncol 8:219-25 (2007) -38 pts treated with Gemcitabine/Cisplatin after anthracycline and taxane pretreatment as (neo)adjuvant, or 1st line met therapy demonstrated a TTP of 5.2 months CI 3.6-6.8 and an OS of 19.5months CI 11.2-27.8 months. Kim JH; Cancer Res Treat 2008; 40: 101-105

2013 Meta-analysis and evaluation

Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. Scarpace SL.

New microtubule-targeting agents.
Review
Further information and references:

Consent:
Carboplatin (vs. Docetaxel): 2++, 11+, 19+/-
Carboplatin in gBRCA mutation: 1++, 26+
Gemcitabin/Cisplatin (vs. GemPac): 1++, 18+, 10+/-

Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:


Gemcitabin/Cisplatin (vs. GemPac)

1. Gemcitabine with cisplatin or paclitaxel in metastatic triple-negative breast cancer. Xichun Hu, Binghe Xu, Li Cai, Zhonghua Wang, Biyun Wang, Jian Zhang, Yuee Teng, Zhongsheng Tong, Yueyin Pan, Yongmei Yin, Changping Wu, Zefei Jiang, Xiaojia Wang, Guyin Lou, Donggeng Liu, Jifeng Feng, Jianfeng Luo, Jiong
2. Wu, Zhimin Shao and Joseph Ragaz San Antonio Breast Cancer Symposium 2014; P3-10-02
Triple negative patients

J Clin Oncol 26: 2008 (May 20 suppl; abstr 1051)
Author(s):
B. Sirohi, M. Arnedos, S. Popat, S. Ashley, A. Nerurkar, G. Walsh, S. Johnston, I. E. Smith
Citation:
Author(s):
J. W. Chia, P. Ang, H. See, Z. Wong, L. Soh, Y. Yap, N. Wong

2013
Met-TNBC Phase II (n=40; RR 35%, med OS 12 m, med TTP 6 m; 27% neutropenia °3/4)

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (13/18)

Further information and references:

Consent:
Cap+Bev as maintenance after Doc+Bev: 1++, 3+, 22+/-, 4-
2nd line as treatment through multiple lines: 19+/-, 4-

Cap+Bev as maintenance after Doc+Bev:


2nd line as treatment through multiple lines:


Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

Review and opinion


Side effects
Metaanalysis:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (14/18)

Further information and references:

Consent:
Taxanes + trastuzumab + everolimus: 4+/-, 21-, 5—


2013

Docetaxel + trastuzumab + pertuzumab (LoE 1bA AGO++)
Baselga et al., December 7, NEJM 2011

Side effects Pertuzumab
Skin rash
Pertuzumab is associated with a significant risk of rash, and the incidence varies among different tumor types. Prevention, early recognition, and appropriate treatment of this rash may lead to improvement in patient quality of life, adherence to therapy, and possibly optimize clinical outcomes.

Paclitaxel + trastuzumab + pertuzumab (LoE 5D AGO+/-)
1st-Line chemotherapy* + trastuzumab (LoE 1bB AGO+)
(*taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel)


Trastuzumab mono (LoE 2bB AGO+/-)

Taxanes + lapatinib (LoE 1b\(^a\) AGO+/-)


Trastuzumab + aromatase inhibitors (if ER+) (LoE 2b\(^b\) AGO+/-)


Lapatinib + aromatase inhibitors (if ER+) (LoE 2b\(^b\) AGO+/-)

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab)

(15/18)

Further information and references:

T-DM1

2. Baselga et al., December 7, NEJM 2011

2013
Capecitabine + lapatinib (LoE 1b B AGO+)


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) (LoE 3b B AGO+)
Trastuzumab plus lapatinib vs lapatinib
Met-HER2posBC phase iii (2nd and further lines; n=291, HR-PFS =0.74, p=0.011; HR OS =0.74, p=0.026)


TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression) (LoE 2b D AGO +)


Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”

**Taxane + trastuzumab + pertuzumab (LoE 5 D AGO +)**

Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab (LoE 5 D AGO +/-)

**Trastuzumab mono (DATEN?) (LoE 2b B AGO +/-)**

2nd line:


1st line:


**Trastuzumab + aromatase inhibitors (if ER+) (LoE 3b B AGO +)**


**Lapatinib + aromatase inhibitors (if ER+) (LoE 3b B AGO +)**

Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2009.23.3734
Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (16/18)

Further information and references:

2013

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel) (LoE 5 D AGO +/-)


Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”


Capecitabine + lapatinib (LoE 2b B AGO +)


**Trastuzumab + lapatinib (if CT not possible) (LoE 3bB AGO +)**


**Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1) (LoE 5D AGO +)**

**EMILIA**

1. Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in

2. HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012


4. Baselga et al., Dec
Lapatinib in HER2-positive Metastatic Breast Cancer (17/18)

Further information and references:

Anthracycline and Taxane and Trastuzumab pre-treatment


Trastuzumab naive patients: first line therapy


Brain metastases (radioresistance)

Immunodiagnostic Tests and Immunotherapy (18/18)

No further information

No references
Osteo oncology and Bone Health
Osteo-oncology and Bone Health

- **Versions 2002-2014:** Bischoff / Böhme / Brunnert / Dall / Diel / Fehm / Fersis / Friedrich / Friedrichs / Huober / Jackisch / Janni / Lux / Maas / Nitz / Oberhoff / Schaller / Scharl / Schütz / Seegenschmiedt / Solomayer / Souchon

- **Version 2015:** Fehm / Hanf
Bisphosphonates in Breast Cancer

- Hypercalcemia
- Reduction of skeletal events (complications)
- Reduction of bone pain
- Treatment beyond progression of bone met’s
- In combination with neoadjuvant chemotherapy
- Prevention of bone metastases/ survival advantage
  - Adjuvant in postmenopausal patients
  - Advanced breast cancer
- Prevention of breast cancer with oral BPs (in women receiving BP for low BMD)

Oxford / AGO LoE / GR

- Hypercalcemia: 1a A ++
- Reduction of skeletal events: 1a A ++
- Reduction of bone pain: 1a A ++
- Treatment beyond progression of bone met’s: 5 D ++
- In combination with neoadjuvant chemotherapy: 2b C +/-
- Prevention of bone metastases/ survival advantage: 1a A +
- Adjuvant in postmenopausal patients: 2b C +/-
- Advanced breast cancer: 2b C +/-
- Prevention of breast cancer with oral BPs (in women receiving BP for low BMD): 2b C +/-
## Denosumab in Breast Cancer

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Oxford/AGO LoE/GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of hypercalcemia</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Reduction of skeletal complications</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Reduction of bone pain</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Increasing bone pain-free survival</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Treatment beyond progression</td>
<td>5 D +</td>
</tr>
<tr>
<td>Progression under bisphosphonates</td>
<td>4 C +/-</td>
</tr>
</tbody>
</table>
# Bone Modifying Agents for the Therapy of Bone Metastases

- Clodronate PO 1600 mg daily
- Clodronate IV 1500 mg q3w / q4w
- Pamidronate IV 90 mg q3w / q4w
- Ibandronate IV 6 mg q3w / q4w
- Ibandronate PO 50 mg daily
- Zoledronate IV 4 mg q4w
- Zoledronate IV 4 mg q12w*
- Denosumab 120 mg s.c. q4w
- Other dosing or schedules, e.g. derived from adjuvant studies or therapy of osteoporosis

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

*for patients after zoledronate iv 4 mg q4w for 1 year or longer
Skeletal Metastases
Treatment with Radionuclids

- Tumor progression after standard treatment of multiple / disseminated metastases and intolerable bone pain (prerequisite: hot spots in the bone scintigraphy)
  - $^{186}$Rhenium-hydroxyethylidene-diphosphonat
  - $^{153}$Samarium
  - $^{89}$Strontium
  - $^{223}$Radium

Cave: Myelosuppression with risks of pancytopenia has to balance potential benefits.
Metastatic Bone Disease of the Spine

Indications for surgery

Oxford LoE: 2b  GR: C  AGO: ++

- Spinal cord compression
  - With progressive neurological symptoms
  - With pathological fractures
- Instability of the spine
- Lesions in pre-irradiated parts of the spine

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!
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
Bone metastases

- With fracture risk
- With functional impairment
- With bone pain
  - Single dose RT = fractionated RT
- With neuropathic bone pain
- Asymptomatic isolated bone metastases

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

*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
  - Oxford LoE: 1b

- Osteonecrosis of the jaw (ONJ) mostly under IV-BP and denosumab therapy (1.3% / 1.8%)
  - Association with (simultaneous) anti-angiogenetic therapies
    - Oxford LoE: 3b

- Severe hypocalcemia (Dmab>BPs)
  - Oxford LoE: 1b

- Acute Phase Reaction*
  - (IV Amino-BPs, Db) 10-30%
  - Oxford LoE: 1b

- Gastrointestinal side effects
  - (oral BPs) 2-10%
  - Oxford LoE: 1b

- Atypical femur fractures
  - Oxford LoE: 2b
    - 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 Bisphosphonates for Reduction of Bone Metastases and Survival Advantage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Postmenopausal Patients</th>
<th>Premenopausal Patients</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate (oral)</strong></td>
<td>1a A</td>
<td>1a +/-</td>
<td></td>
</tr>
<tr>
<td><strong>Aminobisphosphonates (iv or oral)</strong></td>
<td>1a A</td>
<td>1a +/-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></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></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>1b B ++</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>1b A +</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>1b B ++</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>1b A +</td>
</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5 D -</td>
<td></td>
</tr>
<tr>
<td><strong>Regular BMD-measurement recommended</strong></td>
<td>2b B +</td>
</tr>
<tr>
<td><em>(Intervals depending on previous T-values)</em></td>
<td></td>
</tr>
</tbody>
</table>
Further recommendations (based on DVO-guidelines for treatment, diagnosis and prevention of osteoporosis)*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Avoiding immobilisation</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Calcium (1000–1500 mg/d)**</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Vitamine D3 suppl. (800–2000 U/d)</td>
<td>4 C ++</td>
</tr>
<tr>
<td>Cessation of smoking, reduction of alcohol</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Avoiding BMI &lt; 20 mg/m²</td>
<td>3b C ++</td>
</tr>
<tr>
<td>Drugs approved for the treatment of osteoporosis in adults (see next slide)</td>
<td></td>
</tr>
</tbody>
</table>


**if nutritional supply is insufficient, (in combination with Vit D3 only)
## Medical Treatment of Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>70 mg</td>
<td>po/w*</td>
<td></td>
<td>1b B ++</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg</td>
<td>sc/6m*</td>
<td></td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>150 mg</td>
<td>po/m*</td>
<td></td>
<td>1b B ++</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>3 mg</td>
<td>iv/3m</td>
<td></td>
<td>1b B +</td>
</tr>
<tr>
<td>Parathyroid hormone (1-84)</td>
<td>100 µg</td>
<td>sc/d</td>
<td></td>
<td>1b B +</td>
</tr>
<tr>
<td>Raloxifene (improves spine only)</td>
<td>60 mg</td>
<td>po/d</td>
<td></td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35 mg</td>
<td>po/w*</td>
<td></td>
<td>1b B ++</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>2 g</td>
<td>po/d</td>
<td></td>
<td>1b B +</td>
</tr>
<tr>
<td>Teriparatide (1-34)</td>
<td>20 µg</td>
<td>sc/d</td>
<td></td>
<td>1b B +</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>5 mg</td>
<td>iv/12 m*</td>
<td></td>
<td>1b B ++</td>
</tr>
</tbody>
</table>

*Drugs tested in clinical studies with breast cancer patients and tumor therapy-induced osteoporosis

**Elevated risk of myocardial infarction. Substance restricted to postmenopausal pats. with severe osteoporosis and high risk of fractures
### Tabelle 4.2.: Indikation für eine medikamentöse Osteoporosetherapie nach Risikoprofil

In Abhängigkeit von Geschlecht, Lebensalter, DXA-Knochendichte und weiteren Risikofaktoren.\(^1\)

<table>
<thead>
<tr>
<th>Lebensalter in Jahren</th>
<th>T-Score (Nur anwendbar auf DXA-Werte. Die Wirksamkeit einer medikamentösen Therapie ist für periphere Frakturen bei einem T-Score &gt; -2,0 nicht sicher belegt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-2,0 bis -2,5</td>
</tr>
<tr>
<td>Frau 50-60</td>
<td>Nein</td>
</tr>
<tr>
<td>Frau 60-65</td>
<td>Nein</td>
</tr>
<tr>
<td>Frau 65-70</td>
<td>Nein</td>
</tr>
<tr>
<td>Frau 70-75</td>
<td>Nein</td>
</tr>
<tr>
<td>Frau &gt;75</td>
<td>Ja</td>
</tr>
<tr>
<td>Mann 50-60</td>
<td>Nein</td>
</tr>
<tr>
<td>Mann 60-70</td>
<td>Nein</td>
</tr>
<tr>
<td>Mann 65-70</td>
<td>Nein</td>
</tr>
<tr>
<td>Mann 70-75</td>
<td>Nein</td>
</tr>
<tr>
<td>Mann &gt;75</td>
<td>Ja</td>
</tr>
</tbody>
</table>

\(^1\) Alternative Risikomodellierungen können bei Bedarf vergleichend zu Rate gezogen werden (siehe Langfassung).

\(^2\) bei Verwendung eines männlichen Referenzkollektivs für die T-Scores

### Therapieindikation auch schon bei um 1,0 höherem T-Score\(^3\), wenn:

- Glukokortikoide oral \(\geq 2,5\) mg und \(< 7,5\) mg Prednisolonäquivalent tgl. (außer bei rheumatoider Arthritis \(+0,5\))
- Diabetes mellitus Typ 1
- \(\geq 3\) niedrigtraumatische Frakturen in den letzten 10 Jahren im Einzelfall (mit Ausnahme von Finger-, Zehen-, Schädel- und Knöchelfrakturen)
Osteo-oncology and Bone Health (2/19)

No further information

No references
**Bisphosphonates in Breast Cancer (3/19)**

No further information

**References:**

**First three statements:**

*Metaanalysen and Reviews (metastatic breast cancer):*


**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

**Statement: In combination with neoadjuvant chemotherapy**

**Statement: Prevention of bone metastases/ survival advantage**


**Statement: Bisphosphonates - Prevention of breast cancer**


**Denosumab in Breast Cancer (4/19)**

No further information

**References:**

**Denosumab - Therapy of bone metastases and skeletal related complications:**


**Statement: Progression under bisphosphonates**

Bone modifying Agents for the Therapy of Bone Metastases (5/19)

No further information

References:


2. Hortobagyi GN et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. J Clin Oncol 32:5s, 2014 (suppl; abstr LBA9500).

Skeletal Metastasis Treatment with Radionuclids (6/19)

No further information

References:

Reviews / Overview


186Rhenium (186Re-HEDP)


153Samarium (153Sm-EDTMP)


89Strontium (89Sr-Chlorid)


223Ra-dichloride:

Metastatic Bone Disease of the Spine – Indication for surgery (7/19)

Further information:

References:

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


TED-voting of the AGO-group (n=17): ++ n=1; + n=14; +/- n=2
Side-Effects and Toxicity – Bisphosphonates (BP) and Denosumab (Db) (12/19)

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:

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


TED-voting of the AGO-group (n=28): ++ n=0; + n=9; +/- n=18; - n=1

Strontium ranelate

TED-voting of the AGO-group (n=25): ++ n=1; + n=15; +/- n=9
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 2003–2014:**
  Bauerfeind / Bischoff / Böhme / Brunnert / Diel
  / Fehm / Friedrich / Friedrichs / Gerber / Hanf /
  Janni / Lück / Maass / Oberhoff / Rezai /
  Schaller / Seegenschmiedt / Solomayer /
  Souchon

- **Version 2015:**
  Bischoff / Diel
Specific Sites of Metastases

- Liver and lung metastases
- Malignant pleural and pericardial effusions
- Ascites
- Bone marrow involvement
- Soft tissue metastases
- Any other organs

Consider also chapter „CNS Metastases “ and „Locoregional Recurrence (Loco-Regional Recurrence Treatment Options in Non Curative Cases)“
General Aspects of Metastases Surgery or Ablation

- Histological / cytological verification
- Systemic treatment preferred
- Consider surgery only in case of good response to palliative treatment
- Metastases surgery is an option in good condition pts. with late onset oligometastases
- Surgical treatment in the case of pain, exulceration, persistance after systemic treatment, bowel obstruction, hydrocephalus occlusus, spinal cord compression
- Systemic treatment after surgery

* See chapters with systemic treatment recommendations
<table>
<thead>
<tr>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local treatment (R0) of primary tumor</td>
<td>2 B +/-</td>
</tr>
<tr>
<td>Axillary surgery for cN1</td>
<td>5 C +/-</td>
</tr>
<tr>
<td>Sentinel in cN0</td>
<td>5 C -</td>
</tr>
</tbody>
</table>
Liver Metastasis
Local Therapy

- Resection of liver metastasis (R0)
  - Individual cases (liver function) with resectable metastases
  - HR positive; chemotherapy sensible

- Regional chemotherapy

- Regional radiotherapy
  - (SIRT, radiochemoembolization, other modalities)

- Thermoablation
  - (RFA, LITT, cryotherapy)

Oxford / AGO
LoE / GR

3b  C  +/-

4   C  +/-

3b  C  +/-

3b  C  +/-
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VATS or conventional resection</td>
<td>3b</td>
<td>C +/-</td>
</tr>
<tr>
<td>Thermoablation (CT-guided RFA, LITT)</td>
<td>3b</td>
<td>C +/-</td>
</tr>
</tbody>
</table>
Malignant Pleural Effusions (MPE)

Incidence:
- ~ 10 % of all breast cancer patients
- ~ 50 % of pat. with advanced breast cancer
- ~ 30 % of all MPE are caused by breast cancer

Clinical presentation:
- Extensive MPE are mostly due to malignancy
- The majority of MPE are symptomatic
- Survival is related to the presence of additional metastases, age and extent of involving the pleural surface

Diagnostic procedures:
- Clinical examination
- Imaging techniques (chest X-Ray, US, CT-Scan)
- Proven malignant effusion (cytology, histology by thoracoscopy)
Malignant Pleural Effusion (MPE)
Local Therapy

- VATS and Talcum-pleurodesis*  
  1b B  ++
- Chemical pleurodesis
  - Talcum slurry  
    1a B  +
  - Bleomycin, Doxycycline, Mitoxantrone  
    2b C  +/-
  - Povidone iodide  
    3b C  +/-
- Continuous pleural drainage  
  2a B  +
- Systemic treatment after pleurodesis  
  3b C  +/-
- Local antibody therapy (i.e. Catumaxomab)  
  3b C  -
- Repeated pleural drainage  
  5 D  +/-

* Adequate pain-relief
VATS: video-assisted thoracoscopic surgery
Malignant Ascites
Local Therapy

Treatment according to:
Symptoms
Clinical manifestations
Anticipated response to systemic therapy

Ascites:
- Puncture, drainage
- Local chemotherapy
- Systemic therapy
- Local antibody therapy (i.e. Catumaxomab)

Oxford / AGO
LoE / GR

4  D  ++
3b  D  +/-
3b  D  ++
3b  D  +/-
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

<table>
<thead>
<tr>
<th><strong>Capecitabine</strong></th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 D ++</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HER2 pos.: add anti-HER2 Treatment</strong></th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 D ++</td>
<td></td>
</tr>
</tbody>
</table>

* Consider pre-treatment
Radiotherapy (if no immediate surgery is indicated or even after surgery):

- Paresis, spinal cord compression 2b C ++
- Plexus infiltration 3b C ++
- Soft tissue metastasis 3b C +
Specific Sites of Metastases (2/13)

Further information:


Screened guidelines:
NCI (National Cancer Institute , 2013): http://www.cancer.gov
CMA (Canadian Medical Association , 2013): http://www.cmaj.ca

No references
Specific Sites Of Metastases (3/13)

*Further information:*

Specific sites of metastases are liver, lung, pleura, pericard, ascites, bone marrow, soft tissue (muscle, subcutaneous fatty tissue, fascia etc.). Breast cancer metastases in the orbita, adrenals, ovaries, uterus, stomach, colon, gall bladder a.s.o. are very seldom seen clinically. So there are only case reports or series. In such cases treatment options must discussed individual.

*No references*
General Aspects of Metastases Surgery or Ablation (4/13)

Further information:

The systemic treatment of metastatic disease is standard. In general surgery of distant metastases of breast cancer should be considered in patients with a good health condition, oligometastases and a long distance between primary treatment and the occurrence of metastases. (1-5). Good response to palliative treatment may also indicate patients who will benefit from breast surgery. Reported improved overall survival might be the result of patients selection. Before surgery is done metastases should be confirmed as such one by histology. By that a secondary malignancy can be excluded. A re-evaluation of receptor- and HER2-status in metastases is mandatory, because a receptor-shift occurs in nearly 20% with an impact on systemic treatment. Other indications for surgical intervention are symptoms like pain, exulceration or persistence after systemic treatment. Because no data from prospective studies are available, clinicians must weigh retrospective experiences and clinical judgment in deciding whether to offer surgery or techniques for tumor disturbance to these patients. An ongoing trial, E2108 (http://clinicaltrials.gov/show/NCT01242800) has been designed to assess the effect of breast surgery in metastatic patients responding to first-line systemic therapy.

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
Breast Surgery in Primary Metastatic Disease (5/13)

Further information:

The management of primary stage IV (metachronous or primary metastatic) breast cancer focuses on systemic therapy for distant sites. The impact of local treatment extent on overall survival is still under discussion. However retrospective data on more than 30,000 women from North America and Europe have now been published, showing a robust association between surgery or radiotherapy for the primary tumor and prolonged survival.(1) Many questions remain, most importantly, whether this observed association reflects a selection of women with good prognosis for primary site therapy; others relate to the fraction of women in published studies who were diagnosed with metastatic disease postoperatively, whether specific subsets of metastases and biological subtypes would derive greater benefit, and the appropriate timing and extent of local therapy. Depending on the extent of metastatic disease, a local excision of primary tumor or mastectomy with sufficient health margins is recommended.(2-6) An axillary surgery is only indicated for bulky disease. The impact of local radiotherapy on survival is unknown. It should be mentioned, that there are reports, which could not found an advantage regarding overall survival for local surgery in this situation.

References:

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:

Resection of liver metastases should only be performed if histological verification was done, if R0-resection is feasible and no extrahepatic metastases were present. Other procedures like regional radiotherapy as well as thermoablation are indicated in individual cases. The efficacy of the last ones is primarily determined by preablation tumor size and location in relation to the hilum. There are no data to legitimate a regional chemotherapy of liver alone. Mostly a survival benefit for surgery or other ablation techniques have been reported. However this could be the result of patients selection. Diagnostic laparoscopy in combination with intraoperative ultrasound should be planned in future experience.

References:

Resection of liver metastases:


Systemic Reviews:


Regional chemotherapy: (TACE= transarterial chemoembolization)

**SIRT (selective internal radiation therapy):**


**RFA (Radiofrequency ablation):**


**LITT (Laser-induced Thermotherapy):**


**Cyrotherapy:**


Target Therapy

For proven pulmonary metastases, the level of evidence for a curative approach is low, but some patients might benefit from a metastasectomy followed by an appropriate systemic treatment. In accordance with treatment of liver metastases resection of lung metastases should only be performed if R0-resection is feasible and if histological verification was done. Other procedures like thermoablation are indicated in individual cases.

References:

Resection:


**Thermoablation:**


**Radio Frequency Ablation:**

Malignant Pleural Effusion (8/13)

Further information:

Metastatic breast cancer is the second-ranking cause of malignant pleural effusion (MPE), resulting in dyspnoea and reduced subjective well-being. About 10% of all patients develop this clinical complication, in almost 50% of these cases malignant pleural effusion is the first sign of metastatic disease. Median time from primary diagnosis of the cancer to the appearance of pleural effusion is 42 months. It should be treated in symptomatic cases exclusively. Tumor type, extent of involving the pleural surfaces, age and extra-pleural metastases influences the success of a pleurodesis, regardless of the sclerosing agent used. Malignant effusions due to mesothelioma and lung cancer are particularly prone to a failed procedure.

References:

1. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database of Systematic Reviews 2004,
Malignant Pleural Effusion - Local Therapy (9/13)

Further information:

Thoracoscopy with Talcum pleurodesis is the treatment option of choice for malignant pleural effusion. The main procedure for chemical pleurodesis is talcum slurry. Bleomycin, Doxycycline and Mitoxantrone are individual options. Povidone-iodine can be considered as a good alternative to TTP to ensure effective pleurodesis for patients with malignant pleural effusion due to MBC. The drug is available, cost effective and safe, can be given through a thoracostomy tube and can be repeated if necessary. (2) There is no approval for povidone iodide in Germany.

The CALGB trial 9334 showed that bedside talcum pleurodesis was equivalent to thorascopic pleurodesis. Two randomized studies could show that indwelling pleural catheter or tunneled catheter (versus thorascopic pleurodesis) for palliation of malignant pleural effusion is a therapeutic and quality of life sustaining alternative. Retrospectively study confirmed a higher efficacy of pleurodesis followed by systemic treatment may be superior to that of systemic treatment alone with respect to local control of pleural effusions (8.5 versus 4.1 months) in breast cancer patients. Indwelling pleural catheters are indicated in individual cases. Catumaxomab is not recommended because of its side effects.

References:

VATS and talcum-pleurodesis


**Indwelling catheter/pleural drain**


**Antibody therapy:**

Malignant Ascites - Local Therapy (10/13)

Further information:

Malignant ascites are the cancer-associated accumulation of fluids in the peritoneal cavity. The cancers most commonly associated to ascites are ovarian (37%), pancreato-biliary (21%), gastric (18%), oesophageal (4%), colorectal (4%), and breast (3%). After histological confirmation and re-evaluation of receptors the most effective treatment consist in adequate systemic treatment. Management of malignant ascites takes place in the context of palliative care and aims at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains an option in individual cases. It has to be payed attention to the side effects.

References:

Malignant Pericardial Effusion - Local Therapy (11/13)

Further information:

Malignant pericardial effusion and cardiac tamponade remains a rarity, which are known complications of many advanced malignancies such as breast cancer, lung cancer, lymphomas and leukemias. In general overall survival is low, due to other metastatic localizations. The standard treatment of malignant effusion and cardiac tamponade has not yet been defined. Physicians should consider the status and the prognosis of each case. In symptomatic patients drainage and fenestration are the treatment options of choice. VATS is an alternative treatment option. In individual cases US-guided puncture with instillation of mitoxantrone is possible.

References:

Bone Marrow Involvement Associated with Pancytopenia (12/13)

Further information:

The choice between supportive care or specific anticancer treatment for poor performance status (PS) breast cancer patients with multimetastatic disease and pancytopenia due to bone marrow involvement (BMI) often remains a clinical dilemma. If hormonal treatment options have been exhausted, concomitant weekly low-dose chemotherapy (anthracycline, paclitaxel or cabecitabine) and either bisphosphonates or RANK-Ligands antibodies are indicated. Low-dose chemotherapy with epirubicin or paclitaxel as well as treatment with anti-HER2-therapy is the therapy of choice for patients with bone marrow involvement and pancytopenia. Otherwise it has been reported that even in patients with severe BMI-associated cytopenia, aggressive combination treatment regimens were effective, since most patients show improved marrow function after chemotherapy and long-lasting survival is possible.

References:

Soft Tissue Metastasis - Local Radiotherapy (13/13)

Further information:

Local radiotherapy is the most important treatment for patients with paresis or spinal cord compression, who cannot be operated or have failed to systemic treatment. Even after surgery a concomitant radiotherapy and a systemic treatment is indicated. Plexus infiltration and other inoperable soft tissue metastasis should be treated by radiotherapy.

References:

CNS Metastases in Breast Cancer
CNS Metastases in Breast Cancer

- **Versions 2003–2014:**
  Bischoff / Diel / Friedrich / Gerber / Lück / Maass / Müller / Nitz / Jackisch / Jonat / Junkermann / Rody / Schütz

- **Version 2015:**
  Jackisch / Huober
Breast cancer is the 2nd most common cause of CNS metastases

At autopsy:
- Parenchymal CNS metastases: ~30–40%
- Leptomeningeal CNS metastases: ~ 5–16%

Increasing incidence (10 % ⇒ 40 %)

Increasing incidence due to
- More effective treatment of extracerebral sites with improved prognosis
- Increasing use of MRI in diagnostic evaluation

Lack of knowledge about treatment of brain metastases from breast cancer since most studies are not breast cancer specific. Therefore, participation in the german registry study is recommended.
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>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
<td>70-80</td>
<td>90-100</td>
<td>n/a</td>
<td>______</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
<td>LumA</td>
<td>HER2</td>
<td>LumB</td>
<td>______</td>
</tr>
<tr>
<td>Age, years</td>
<td>&gt; 60</td>
<td>&lt; 60</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>______</td>
</tr>
<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
## Independent Prognostic Factors in BM

### Multivariate analyses of significant factors associated with survival after WBRT

- OS in 1, 2 and 3 years was 33.4 %, 16.7%, and 8.8 %
- Median survival time by Recursive partitioning analysis (RPA) class in months: Class I: 11.7, class II: 6.2 and class III: 3.0

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>P</th>
<th>HR</th>
<th>(95%-confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURGICAL RES</td>
<td>&lt;0.0001</td>
<td>4.34</td>
<td>2.5</td>
</tr>
<tr>
<td>SINGLE METASTASES</td>
<td>0.14</td>
<td>1.08</td>
<td>0.97</td>
</tr>
<tr>
<td>KPS &gt;= 70</td>
<td>0.55</td>
<td>1.31</td>
<td>0.55</td>
</tr>
<tr>
<td>BRAIN MET SCORE (BS-BM)</td>
<td>0.58</td>
<td>0.63</td>
<td>0.12</td>
</tr>
<tr>
<td>RPA</td>
<td>&lt;0.0001</td>
<td>1.64</td>
<td>1.32</td>
</tr>
<tr>
<td>CONTR PRIM TU</td>
<td>0.66</td>
<td>0.92</td>
<td>0.63</td>
</tr>
<tr>
<td>NO EXCRANIAL MET</td>
<td>&lt;0.0001</td>
<td>2.38</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Viani GA et al. BMC Cancer 2007, 7:53
Brain Metastases (1–3 Lesions)

WBRT + SRS boost or neurosurgery (vs. WBRT)
Improved local control rate

SRS (lesions < 3 cm) or neurosurgery +/- WBRT*

WBRT**
Stereotactic fractionated RT (SFRT)

* In individual cases additional WBRT may be omitted. Additional WBRT provides improved local control rate and symptom control but not survival benefit in all patient cohorts. Combined treatment is recommended especially in patients with single brain metastases and good performance status.

** In patients with poor prognosis and / or performance status

SRS = stereotactic radiosurgery
WBRT = whole brain radiotherapy
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 > ~ 3 cm not allowing stereotactic radiosurgery
- Surgically favorable location

Factors in favor of primary radiotherapy:

- No need for rapid decompression
- No need for histological verification
- Tumor location poorly amenable to surgery
Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952- 26001 Study

<table>
<thead>
<tr>
<th>2-year relapse rate after whole-brain radiotherapy (WBRT) versus observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>after surgical resection (n=160)</td>
</tr>
<tr>
<td>WBRT</td>
</tr>
<tr>
<td>Local recurrence</td>
</tr>
<tr>
<td>New lesions</td>
</tr>
</tbody>
</table>

- Only 12% of the patients had brain metastases from breast cancer.
- Overall survival was similar in the WBRT and observation arms (median, 10.9 vs. 10.7 months, respectively; P = .89).
- Intracranial progression caused death in 44% patients in the OBS arm and in 28% patients in the WBRT arm.

Kocher M. J Clin Oncol 2011, 29:134-141
## Multiple Brain Metastases (>3 Lesions)

- **WBRT (add corticosteroids*)**
  - Prolonged RT (≥ 1 week)
- **Radiochemotherapy**
- **Chemotherapy alone**
- **Corticosteroids alone**

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

*Symptom adjusted therapy

**In case of radioresistance / recurrence:**

- **Chemotherapy alone**
- **Lapatinib +/- Capecitabine (HER2 pos. disease)**
- **T-DM1 (HER2 pos. disease)**
- **Re-radiation (if feasible)**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a D +/-</td>
</tr>
<tr>
<td>2b B +</td>
</tr>
<tr>
<td>2b B +</td>
</tr>
<tr>
<td>3a D +/-</td>
</tr>
</tbody>
</table>
Possible Treatment Approach for Brain Metastases (BM) in Breast Cancer*

**Single BM**
- Controlled extra-CNS disease and KPS ≥ 70
- Extra-CNS disease not controlled or KPS < 70

**BM ≤ 3**
- Controlled extra-CNS disease and KPS ≥ 70
- Extra-CNS disease not controlled or KPS < 70

**BM > 3**
- Controlled extra-CNS disease + KPS ≥ 70

- Surgery or RS or SRT ± adjuvant WBRT
- SRT ± adjuvant WBRT ± sequential systemic CT
- Surgery or RS/SRT ± adjuvant WBRT ± sequential systemic CT
- WBRT ± systemic CT
- WBRT ± surgery ± RS/SRT ± systemic CT

BM: brain met.  CT: chemotherapy  RS: radiosurgery  SRT: stereotactic radiotherapy  WBRT: whole brain radiotherapy

*Adapted from Bertolini F et al. CNS Oncology 2015;4(1):37-46*
## Systemic and Symptomatic Therapy of Brain Metastases

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue anti-HER2-treatment in case of extracranial remission (HER2 pos. disease)</td>
<td>2c</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Lapatinib + Capecitabine as initial treatment (HER2 pos. disease)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Chemotherapy alone as primary treatment</td>
<td>3</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>Routine prophylactic use of anticonvulsants</td>
<td>3</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Glucocorticoids (only when symptoms and/or mass effect)</td>
<td>3</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>
# Leptomeningeal Carcinomatosis

## Local Therapy

### Intrathecal or ventricular therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LoE</th>
<th>Grade</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>
</tbody>
</table>

### Radiotherapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<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 (2/13)

No further information

No references
CNS Metastases in Breast Cancer – Incidence (3/13)

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:


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

(5/13)

No further information

References:

References for Breast-GPA:


Further References: Prognostic Factors for Survival:


Independent Prognostic Factors in BM (6/13)

No further information

Reference:

Brain Metastases (1-3 lesions) (7/13)

No further information

References:


Possible Factors for Decision-Making Neurosurgery versus Stereotactic Radiosurgery (8/13)

No further information

No references
Adjuvant Whole-brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study (9/13)

No further information

Reference:

Multiple Brain Metastases (10/13)

No further information

References:


Re-Radiation


Radiochemotherapy

Possible treatment Approach for Brain Metastases in Breast Cancer (11/13)

No further information

Reference:

Systemic and Symptomatic Therapy of Brain Metastases (12/13)

No further information

References:


Chemotherapy


Anticonvulsants

**Steroids**

Leptomeningeal Carcinomatosis Local Therapy (13/13)

No further information

References:


**Trastuzumab intrathecal**


**MTX high dose**

Complementary Therapy

Survivorship
Complementary Therapy – Hormonal Treatment and Alternatives in Breast Cancer Survivors – Survivorship

- **Version 2002–2014:**
  Albert / Bauerfeind / Blohmer / Fersis / Friedrich / Gerber / Göhring / Hanf / Janni / Kümmel / von Minckwitz / Oberhoff / Scharl / Schmidt / Schütz / Thomssen

- **Version 2015:**
  Hanf / Kümmel
### CAM
**Complementary + alternative medicine**

<table>
<thead>
<tr>
<th>Complementary</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to scientifically based medicine</td>
<td>Instead of scientifically based medicine</td>
</tr>
</tbody>
</table>

### UCT
**Unconventional Thx**

<table>
<thead>
<tr>
<th>Unconventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unproven outsider methods</td>
</tr>
</tbody>
</table>
General considerations

- Alternative methods (CAM) instead of surgical treatment
  - Oxford AGO LoE / GR 5 D --

- Alternative methods (CAM) instead of systemic treatment
  - 2b B --

- 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)  
  2b B +/-
- Acupuncture (nausea, vomiting)  
  2b B +
- Early postop. exercise reduces upper-limb dysfunction (beware: increased wound drainage)  
  1a A +
- Prophylactic lymph drainage  
  1b B -
Complementary Treatment Impact on Toxicity I

While on anti-cancer treatment: beware of drug interactions

- **Mistletoe** (*Viscum album*) in order to reduce side effects (influence on efficacy of anti-tumor therapy unknown)
- **Thymic peptides** (lowered risk of severe infections) (influence on efficacy of anti-tumor therapy unknown)
- **Ginseng** (in order to reduce cancer related fatigue) (note: ginseng inhibits cytochrome P enzymes e.g. CYP 3A4)
- **Ganoderma Lucidum**
- **L-Carnitine** (given for prevention of toxicity, increased chemotherapy induced peripheral neuropathy)
- **L-Carnitine does not improve cancer rel. fatigue**
- **Curcumin as an adjunct to reduce radio dermatitis**
- **Ginger for chemotherapy induced nausea & vomiting** (consider interaction with anti-tumor drugs)

Oxford / AGO
LoE / GR

---

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

While on anti-cancer treatment: beware of drug interactions
### Complementary Treatment Impact on Toxicity II

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

Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Effect</th>
<th>Grade</th>
<th>Level</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese medicinal herbs</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>Homoeopathic medicines</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Topical Silymarin</td>
<td>3a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Pain</td>
<td>1a</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>
Complementary Treatment
Mind-Body Medicine I

MBSR (Mindfulness-Based Stress Reduction)
Programme improves quality of life, coping strategies, attentiveness, lowers stress and depressive syndromes

Physical exercise / sport
min. 150 min. moderate endurance training per week in combination with work out exercises (2x per week) improve quality of life, cardio-respirat. fitness, physical performance and fatigue, no higher risk of lymphedema
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

Yoga: 1b A +
Qi Gong: 2a B +/
Tai Chi: 2a B +/
Hypnosis: 1b A +
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)
  - Oxford /AGO LoE / GR
    - 1a A ++

- Low fat diet (improves prognosis – DFS and OS)
  - dietary counseling recommended,
  - 1a A +

- Avoid high-fat dairy products
  - 2b C +

- Flaxseed/increased fibre intake
  - 2a B +

- Adherence to general nutrition guidelines (e.g. DGE, WCRF)
  - 2a B ++

- Dietary extremes (are associated with less favourable outcomes)
  - 1b B - -
Complementary Treatment
Prevention of Recurrence III
Dietary Supplements – Herbal Therapies

Post treatment vitamin/antioxidant supplements doesn't appear to be associated with increased risk of recurrence (beware of drug/treatment interactions)
Smokers on antioxidant supplements are at higher risk for lung cancer

- For Prevention of BC Recurrence:
  - Antioxidants
  - Orthomolecular substances
    (Selenium, Zinc...)
  - Vitamin supplementation in pats on a balanced diet (esp. Vit C, E, D)
    - Artificial carotenoids appear to be associated with worse outcome
  - Proteolytic enzymes
    (Papain, Trypsin, Chymotrypsin)
  - Soy-food (natural source of phytoestrogenes)
    - Concentrates containing ≥ 100 mg) isoflavones
  - Black Cohosh (Cimicifuga racemosa)
  - Mistletoe (Viscum album)
  - Thymic peptides (impact on OS)
  - Oxygen- and ozone therapy
  - Antioxidant supplements (after completion of radiotherapy)
  - Laetrile
  - Cancer bush (Sutherlandia frutescens), Devil's claw
    (Harpagophytum procumbens), Rooibos tea (Aspalathus linearis),
    Bambara groundnut (Vignea subterranea)

Oxford AGO
LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post treatment vitamin/antioxidant supplements</td>
<td>2b</td>
<td>B +/-</td>
</tr>
<tr>
<td>Smokers on antioxidant supplements</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>For Prevention of BC Recurrence:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Orthomolecular substances</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Vitamin supplementation in pats on a balanced diet</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Proteolytic enzymes</td>
<td>3b</td>
<td>B -</td>
</tr>
<tr>
<td>Soy-food (natural source of phytoestrogenes)</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Black Cohosh (Cimicifuga racemosa)</td>
<td>2a</td>
<td>B +/-</td>
</tr>
<tr>
<td>Mistletoe (Viscum album)</td>
<td>1b</td>
<td>C -</td>
</tr>
<tr>
<td>Thymic peptides (impact on OS)</td>
<td>2a</td>
<td>B -</td>
</tr>
<tr>
<td>Oxygen- and ozone therapy</td>
<td>5</td>
<td>D -</td>
</tr>
<tr>
<td>Antioxidant supplements (after completion of radiotherapy)</td>
<td>2b</td>
<td>B +/-</td>
</tr>
<tr>
<td>Laetrile</td>
<td>1c</td>
<td>D -</td>
</tr>
<tr>
<td>Cancer bush (Sutherlandia frutescens), Devil's claw</td>
<td>5</td>
<td>D -</td>
</tr>
</tbody>
</table>
Complementary Treatment
Cancer Pain Reduction

- Acupuncture for cancer pain in adults
- Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults
- Cave: No delay in diagnostic process
Complementary Therapy – Survivorship (2/14)

Further information:

Screened Data Sources:
Pubmed 2003 - 01/2015

ASCO 2003 – 2014
SABCS 2003 – 2014
EBCC 2003 – 2014
Cochrane library: summary Jan. 2015:

External advice:

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: Prof. Dr. G. Dobos and team, Alfried Krupp von Bohlen und Halbach-Stiftungsprofessur für Naturheilkunde an der Universität Duisburg-Essen, Klinik für Innere Medizin V, Naturheilkunde und Integrative Medizin

No references
Alternative Therapies (3/14)

Further information:

The term „alternative therapies“ has to be more precisely defined. The above scheme divides the subject into two main aspects:

- UCT refers to unconventional therapies with unproven methods; they frequently include outsider methods with possible considerable inherent risks.
- CAM includes both alternative therapies, which are used instead of conventional, scientifically based medicine, and complementary methods, which are used in addition to conventional methods. While conventional clinicians tend to more readily approve of the complementary approach than one of the other options, complementary approaches, if administered simultaneously with conventional therapies, always carry the risk that the treatments unexpectedly interfere with each other to produce untoward effects, i.e., drug interactions with partially incalculable outcomes.

No References
General Considerations (4/14)

No further information

References:


Complementary Therapy Pre- and Postoperative (5/14)

No further information

References:

Hypnosis


Acupuncture and Postoperative Nausea and Vomiting


**Postoperative exercise**


**Prophylactic lymph drainage**

Complementary Treatment. Treatment phase. Impact on Toxicity I (6/14)

No further information

References:

Mistletoe:


Thymus:

Ginseng, Ganoderm lucidum:

Abstimmungsergebnis der AGO-Empfehlung: einstimmig

L-Carnitine:


Abstimmungsergebnis der AGO-Empfehlung: einstimmig
Curcumin:


Abstimmungsergebnis der AGO-Empfehlung: 15/5
Complementary Treatment. Treatment phase. Impact on Toxicity II (7/14)

No further information

References:

Antioxidant supplements


Vitamin C


Selen


Coenzym Q10


Proteolytic enzymes and toxicity of chemotherapy:

Bromelain


Chinese herbal medicine and wound healing

Additional Complementary Therapy Side Effects Related to Cancer Treatments - e.g. Chemotherapy (8/14)

No further information

References:

Chinese medicinal herbs


Homeopathic medicines for adverse effects of cancer treatments


Topical use of Silymarin

Acupuncture


Chemotherapy-induced Nausea and Vomiting


Cognitive dysfunction

Fatigue


Pain


Leucopenia

References:

Mind-Body Medicine (MBM)


MBSR


Physical exercise


Statement on quality of life


**Cardio respiratory Fitness / Physical Functioning**


Fatigue

Complementary Therapies - Mind-Body-Medicine II (10/14)

No further information

References:

Yoga


**Qigong**


**Tai Chi**


Tai Chi Abstimmungsergebnis der AGO-Empfehlung: 10/7

Hypnosis


Hypnosis: Abstimmungsergebnis der AGO-Empfehlung: 12/9
Modifiable Lifestyle Factors – Nutrition after Breast Cancer Diagnosis – Prevention of Recurrence II (11/14)

No further information

References:

Physical exercise


**Improvements in DFS and OS, prevention of recurrence**


**Smoking**


**Smoking: Abstimmungsergebnis der AGO-Empfehlung: 10/5**


**Alcohol**

49. Reding et al.: Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young women. Cancer Epidemiol Biomarkers Prev. 2008; 17: 1988-1996. These results suggest that women who consume alcohol before a 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:

Gynecological Issues in Breast Cancer Patients
Gynaecologic Issues in Breast Cancer Patients

- Version 2015:
  Loibl / Gerber
  (with contribution from Hanf / Kümmel und Stickeler / Scharl)
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
  - Estradiol during AI therapy

*Study participation recommended*
Alternative Medical Approaches to Reduce Menopausal Symptoms

**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

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Oxford / AGO
LoE / GR

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1a A +
1b A +/-
1b A +/-
1a A +
1b A +/-
1b A +
1b A +/-
1b A -
“Herbal” Approaches to Reduce Menopausal Symptoms

While anti-cancer treatment: Beware of drug interactions!

<table>
<thead>
<tr>
<th>Herbal Approach</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-derived phytoestrogens – isoflavonoids (might stimulate BC especially in endocrine responsive disease)</td>
<td>1b A -</td>
</tr>
<tr>
<td>Flaxseed-supplementation (40 g/d) (in HR+ ≤ 10 g/d) (reduces relapses no effect on hot flashes)</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Black Cohosh for hot flushes</td>
<td>1b A -</td>
</tr>
<tr>
<td>Black cohosh + St. John’s Worth</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>St. John’s Wort (in combination-therapy) (pharmacokinetic interference with endocrine therapy, cytotoxic drugs and tyrosin kinase inhibitors)</td>
<td>1b B --</td>
</tr>
<tr>
<td>Kava-Kava (Piper methysticum)</td>
<td>5 D --</td>
</tr>
<tr>
<td>Red Clover leaf (Trifolium pratense)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Dong Quai root (Angelica sinensis)</td>
<td>5 D --</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>
Alternative General Approaches to Reduce Menopausal Symptoms after BC I

General approaches:

- Physical exercise: 1b B +
- Mind Body-medicine (yoga, hypnosis, education, counselling): 1b B +
- Cognitive behavioral therapy (CBT): 1b B +
- Acupuncture:
  - Aromatase-inhibitor treatment induced arthralgia: 2b B +
  - Hot flashes: 1b B +
  - Depression: 2b B +/-
  - Anxiety, Sleep: 3b C +/-

(take note: no acupuncture in tumor bearing region, possibility of cell seeding)
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (CT)

- Ovarian Function Protection
- CT + GnRHa (Interaction with CT unclear) 1b B +/- (GnRHa application > 2 weeks prior to chemotherapy)

Impairment of CT – effect cannot be excluded!

- Fertility preservation counselling 4 C +
- Fertility preservation with assisted reproduction therapy 4 C +
# Ovarian Function Preservation – Comparison of Randomized Trials

<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

Vorteil GnRHa / Vorteil Kontrolle

nach Del Mastro et al. Cancer Treat Rev 2014
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 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>
<tbody>
<tr>
<td>FSH (follicle stimulating hormone) plus estradiol</td>
<td>• Serum level on cycle day 2–3&lt;br&gt;• Variation between cycles possible&lt;br&gt;• High FSH value is associated with poor response to ovarian stimulation</td>
</tr>
<tr>
<td>Anti Müllerian Hormone (AMH)</td>
<td>• No specific timing for the test&lt;br&gt;• Stable value within and between menstrual cycles&lt;br&gt;• Low AMH value is associated with poor response to ovarian stimulation</td>
</tr>
<tr>
<td>Antral follicle count (AFC)</td>
<td>• Number of visible follicles (2–10 mm) during transvaginal ultrasound&lt;br&gt;• Performed on cycle days 2–5&lt;br&gt;• Number of antral follicles correlates with ovarian response to stimulation</td>
</tr>
</tbody>
</table>

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

- **Barrier methods**
- **Sterilization (tubal ligation / vasectomy)**
- **Non-hormonal intrauterine devices (IUDs)**
- **Levonorgestrel-releasing IUDs**
  - **Removal in newly diagnosed patients**
- **Timing methods**
- **Injectable progestin-only contraceptives**
- **Progestin-only oral contraceptives**
- **Combined oral contraceptives**

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>5 D +</th>
<th>5 D +</th>
<th>5 D +</th>
<th>4 D +/-</th>
<th>5 D -</th>
<th>5 D -</th>
<th>5 D -</th>
<th>5 D -</th>
</tr>
</thead>
</table>

No trial included women after diagnosis of breast cancer, non-estrogen containing devices do not increase the risk to develop primary breast cancer.
Gynecological Issues in Breast Cancer Patients (2/12)

No further information

No references
Hormonal (Replacement) Therapy of Estrogen Deficiency after Diagnosis of Breast Cancer (3/12)

No further information

References:

- 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:

Alternative Medical Approaches to Reduce Menopausal Symptoms (4/12)

Further information:

Menopausal symptoms are bothersome for breast cancer survivors and affect quality of life. Since hormonal replacement therapy should be avoided in ER positive breast cancer patients alternatives are important. In breast cancer patients treated with tamoxifen and menopausal symptoms the use of venlafaxine, citalopram, clonidine, gabapentin and pregabalin is considered effective in treating hot flashes. (L'Espérance S, 2013) The use of paroxetine and fluoxetine should be avoided because the may reduce the efficacy of tamoxifen. Patients not being treated with tamoxifen the use of venlafaxine, paroxetine, citalopram, clonidine, gabapentin and pregabalin be considered effective in treating hot flashes. Breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes. (Bordeleau L, 2010) For urogenital problems vaginal moisturizers or topical estrogens can be used (Loibl S, 2011). Sertraline, phytoestrogens, black cohosh and St. John's wort should not be used to treat hot flashes. (L'Espérance S, 2013; Kontos M, 2010)

References:

SSRI:

**Venlafaxine**


**Desvenlafaxine**


**Paroxetine**


**Fluoxetine**


**Citalopram**


**Gabapentin**


**Pregabalin**


**Clonidin**


**(D) MPA (depo-) (Medroxyprogesterone acetate)**


Vitamine E


“Herbal” Approaches to Reduce Menopausal Symptoms (5/12)

Further information and references:

The majority of studies, regarding the efficacy of herbal treatments for menopausal symptoms – mostly hot flushes – have not been conducted in women with breast cancer and many are of short duration. (Roberts H, 2010) Increased pharmacovigilance practices for herbal medicines are required with initiatives to stimulate reporting of suspected adverse reactions. Red clover users were less likely to report weight gain, night sweats, and difficulty concentrating. (Ma H, 2011)


Soy-derived isoflavonoids are potent phytoestrogens, which can interact with estrogen receptors, and their dose-response relationships with estrogen receptors in vitro are complicated.


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 Dong Quai (Zhuang SR) nor Ginseng root (Kim MS. 2013) showed a benefit regarding improvement of menopausal symptoms. In a Phase III trial the fixed combination of Red Clover and St. Johns Wort were significantly better in reducing menopausal symptoms than placebo.


In a recent randomised placebo controlled trial in 72 non breast cancer women suffering from hot flashes 40mg red clover leaves showed a significant reduction in hot flashes based on the menopausal rating scale compared to placebo.(Shakeri F, 2015)


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

**Alternative General Approaches to Reduce Menopausal Symptoms after BC I (6/12)**

**Further information:**

Physical exercises (PE) and cognitive behavioral therapy (CBT; this is one form of psychotherapy) have positive effects on menopausal symptoms and, to a lesser degree, on sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause. (Duijts SF, 2012; Pachman DR, 2010; Mann E, 2012) Mind-Body-Medicine (MBM; Relaxation training, Yoga, Hypnosis) resulted in a moderate up to a significant improvement in hot flashes score, joint pain, fatigue, sleep, mood, and relaxation. (Buffart LM, 2012; Cramer H, 2014) However these effects are seen even after a longer period of application and avoid after some months stopping MBM. Acupuncture can also be used but the results from RCT are conflicting. A meta-analysis showed significant effects of acupuncture compared with sham acupuncture, but marked heterogeneity was observed in this model. (Lee MS, 2009)

**References:**

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving Adjuvant Chemotherapy (7/12)

Further information:

Fertility preservation counselling is suggested in all patients who want to preserve their fertility.

References:

Randomised Controlled Trials and Metaanalysis


Ovarian Function Preservation Comparison of Randomized Trials (8/12)

No further information

No references
Metaanalysis of GnRHa for Prevention of Premature Ovarian Failure (9/12)

No further information

No references
**Testing Ovarian Reserve (10/12)**

**Further information:**

The menstruation history is reliable only in women < 45 years of age. A more precise evaluation, especially in perimenopausal patients is possible with the measurement of FSH and E2 levels in peripheral blood. Hormonal replacement should be stopped at least 6 weeks before measurement. In perimenopausal women undergoing treatment for breast cancer, it can be difficult to determine true menopausal status because adjuvant chemotherapy, tamoxifen, and gonadotropin-releasing hormone analogues can induce transient (or permanent) ovarian suppression [1,2]. Low AMH (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 (11/12)

No further information

No references
Contraceptive Options for Women after Diagnosis of Breast Cancer (12/12)

No further information

References: