Breast Cancer:
Specific Situations

Screened data bases:

Screened Guidelines:
3. https://www.esmo.org/guidelines/breast-cancer
4. ASCO (American Association of Clinical Oncology, Practice Guidelines) http://www.asco.org
5. CMA (Canadian Medical Association): http://www.cmaj.ca
6. NCCN (National Comprehensive Cancer Network) vs. 5/2023: http://www.nccn.org
Breast Cancer:
Specific Situations

- **Versions 2005–2023:**
  - Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring / Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass / Mundhenke / Müller / Oberhoff / Rody / Scharl / Schmidt / Schneeweiss / Schütz / Sinn / Solomayer / Stickeler / Thomssen

- **Version 2024**
  - Harbeck / Sinn / Thomssen

Screened data bases:

Screened Guidelines:
3. https://www.esmo.org/guidelines/breast-cancer
4. ASCO (American Association of Clinical Oncology, Practice Guidelines) http://www.asco.org
5. CMA (Canadian Medical Association): http://www.cmaj.ca
6. NCCN (National Comprehensive Cancer Network) vs. 5/2023: http://www.nccn.org
Content – Specific Situations

- Young patients ≤ 40 years
- Pregnancy and breast feeding-associated BC
- Elderly patients
  - Geriatric assessment
- Male patients
- Inflammatory breast cancer (IBC, cT4d)
- Occult breast cancer - axillary CUP (“Cancer of Unknown Primary”)
- Paget’s disease
- Malignant and Borderline Phyllodes-Tumor
- Sarcoma, Angiosarcoma
- Metaplastic breast cancer
Breast Cancer in Young Women ≤ 40 Years

<table>
<thead>
<tr>
<th>Oxford LoE</th>
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<tr>
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<tr>
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</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>


Prognosis in young women


7. 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


3. 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

Temporäre ET Unterbrechung im Kinderwunsch zu realisieren

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 – Diagnostics and Surgery

- Breast imaging and biopsy like as in non-pregnant patients (no general indication for MRI)
  - Oxford LoE GR AGO
  - 4 C ++
- Staging if indicated (bone scan after delivery)
  - 5 D +
- Full body MRI (without contrast agent)
  - 4 C +/-
- Surgery like in non-pregnant patients
  - 4 C ++
- Sentinel node excision (technetium only)
  - SLNE during 1st trimester
  - Sensitivity and specificity not established (during lactation); breast feeding should be avoided for 24 hrs
  - Blue dye (not tested in pregnant animals or humans)
  - 2a B +
  - 5 D +/-
  - 4 C ++
  - 4 C --

* Participation in register study recommended

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

Outcome information (e.g. GBG registry)
**Statement: Breast imaging & biopsy like in non-pregnant**

**Statement: Staging: ultrasound, chest X-ray if indicated**

**Statement: Whole Body MRI**

**Statement: Surgery like in non-pregnant patients**

**Statement: „Sentinel node biopsy“ during pregnancy**

Reviews
General principles

Statement: Radiotherapy during pregnancy

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

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

<table>
<thead>
<tr>
<th>Radiation therapy during pregnancy</th>
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<tr>
<td>(Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)</td>
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<td></td>
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<tr>
<td>Anthracyclines: AC</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Dose-dense regimens with short-acting G-CSF</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Taxanes</td>
<td>2a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Platinum salts (carboplatin, cisplatinum)</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>MTX (e.g. CMF)</td>
<td>4</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>Endocrine treatment</td>
<td>4</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>HER2-targeted treatment</td>
<td>3a</td>
<td>C</td>
<td>--</td>
</tr>
<tr>
<td>Checkpoint inhibitors</td>
<td>4</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td>Bisphosphonates, denosumab</td>
<td>4</td>
<td>D</td>
<td>--</td>
</tr>
</tbody>
</table>

Treatment (Chemotherapy, surgical procedure and radiotherapy) of patients with breast cancer during pregnancy should be as similar as possible to standard treatment of young, not pregnant patients with breast cancer.

Statement: Anthracyclines: AC, EC

Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy

Statement: Taxanes


**Statement: Platinum salts**


**Statement: MTX (e.g. CMF)**


**Statement: Endocrine treatment**


Statement Trastuzumab during pregnancy
13. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Lambertini M, et al. Cancer. 2019

Statement Immunotherapy during pregnancy
Statement Bisphosphonate during pregnancy

General information: Chemotherapy during pregnancy
Breast Cancer During Pregnancy* or Breast Feeding – Delivery and Breast-Feeding

- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)
  - LoE 2b, GR C, AGO ++

- Termination of pregnancy does not improve maternal outcome
  - LoE 3b, GR C

- Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir
  - LoE 4, GR C, AGO ++

- If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities
  - LoE 5, GR D, AGO ++

- Participation in register study recommended

General principles

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 in leucocyte nadir
Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities
1. Williams Obstetrics lecture book
Breast Cancer and Pregnancy* or Breast Feeding – Family Planning

7. Oktay K et al. Increased chemotherapy-induced ovarian reserve loss in women with germline BRCA mutations due to oocyte deoxyribonucleic acid double strand break repair deficiency. Fertil Steril 2020;113:1251–1260
9. Grynberg M et al. BRCA1/2 gene mutations do not affect the capacity of oocytes from breast cancer candidates for fertility
Breast Cancer During Pregnancy* and Breast Feeding - Outcome -

- BC during pregnancy
  - Prognosis is not worse if adequately treated 3a

- BC during lactation and within the first year after pregnancy
  - Prognosis worse than in BCP and if unrelated to pregnancy 3a

- Pregnancy / lactation after BC
  - Outcome not compromised 3a

* Participation in register study recommended

General principles

Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately
Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

1. Gelber S et al. Effect of pregnancy on overall survival after diagnosis of early stage breast cancer. JCO 2001; 19: 1671-5: IBCSG-participants - matched pair analysis: 94 patients pregnant after treatment (RR 0.44 – 0.96; p=0.04).

Review articles
## Treatment for Fit Elderly Patients
*(Life Expectancy > 5 yrs. and Acceptable Comorbidities)*

<table>
<thead>
<tr>
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</table>

### Clinical geriatric assessment
- Surgery similar to "younger" age
- Endocrine treatment (HR+)
- Chemotherapy (standard regimens)
  - ≤ 70 years
  - > 70 years (especially N+, ER / PR-)
- Radiotherapy
- Omit radiotherapy after BCS if low-risk, and if endocrine treatment is administered
- Anti-HER2-therapy

* Study participation recommended

---


**Statement: Treatment according to standard**

Statement: Surgery similar to „younger“ age
Statement: Endocrine treatment (endocrine resp.)
7. 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
3. Fargeot P: Disease-free survival advantage of weekly epirubicin plus tamoxifen versus tamoxifen alone as adjuvant treatment of operable, node-positive, elderly breast cancer patients: 6-year follow-up results of the French adjuvant study group 08 trial.J Clin Oncol. 2004 Dec 1;22(23):4622-30

Statement: Chemotherapy in pts. > 70 years
3. Schmidt M, Nitz U, Reimer T et al. Adjuvant capecitabine versus nihil in elderly patients with moderate or high-risk early breast cancer receiving ibandronate – The ICE Randomized Clinical Trial. Submitted

Statement: Radiotherapy
2. Sautter M.L et al When are breast cancer patients old enough for the quitclaim of local control Strahlenther Onkol 2012 :1-5

Statement: Trastuzumab
4. Tan-Chiu E: Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by
paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005 Nov 1;23(31):7811-9


### Treatment for Frail Patients

*(Life Expectancy < 5 yrs., Substantial Comorbidities)*

- **Reduced standard treatment**
- **Options extrapolated from trials in elderly:**
  - No breast surgery (consider endocrine therapy)
  - No axillary clearing (≥ 60 y, cN0, HR-pos)
  - No radiotherapy (Tumor size < 3 cm, pN0, HR-pos)
  - Hypofractionated radiotherapy
  - No chemotherapy if > 70 yrs. and negative risk-benefit analysis

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<td>2b</td>
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</table>

1. Walzer DE Measuring the value of radiotherapy in older women with breast cancer J Clin Oncol 2012 30 (23) 2809-2811
2. Audisio RA et al When reporting on older patients with cancer, frailty information is needed Ann Surg Oncol 2011; 18: 4-5
3. Smith BD et al Improvement in breast cancer outcomes over time: are older missing out? J Clin Oncol 2011 29 (35) 4647-4653
4. Hughes KS et al Lumpectomy plus tamoxifen with or without irradiation in women age 70 or older with early breast cancer 2010 J Clin Oncol 28:69s (suppl 15, abstr 507).

**Statement: Reduced standard treatment**

**Statement: No breast surgery (consider endocrine options)**


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


Statement: No radiotherapy (≥ 70 y, pT1, pN0, ER+)


5. Fyles AW: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004 Sep 2;351(10):963-70


Statement: Hypofractionated radiotherapy

Statement: No chemotherapy > 70 years and negative risk benefit analysis


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

**International registry**


**General**


<table>
<thead>
<tr>
<th>Diagnostic work-up as in women</th>
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<tr>
<td>Mammography</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Standard-surgery: Mastectomy</td>
<td>4</td>
<td>C</td>
<td>+++</td>
</tr>
<tr>
<td>BCT is an option (tumor / breast relation)</td>
<td>4</td>
<td>C</td>
<td>+**</td>
</tr>
<tr>
<td>Sentinel-node excision (SLNE)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In occult breast cancer</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Radiotherapy as in women</td>
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<td>C</td>
<td>+</td>
</tr>
<tr>
<td>(consider tumor / breast relation!)</td>
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<tr>
<td>Genetic counseling (see genetics chapter)</td>
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<td>B</td>
<td>++</td>
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<tr>
<td>Screening for 2nd malignancies according to guidelines</td>
<td>GCP</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

* Treatment in certified breast cancer centers recommended; ** Participation in register study recommended

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**Guidelines Breast Version 2024.1E**

Website: [www.ago-online.de](http://www.ago-online.de)

Statement: Diagnostic work up as in women

Statement: Mammography

Statement: Ultrasound

Statement: Standard-surgery: Mastectomy – men


Statement: Sentinel-node excision (SNE)

Statement: Radiotherapy as in women (consider tumor breast relation!)

Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer)
1. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26

Statement: Screening for 2nd malignancies according guidelines

Statement: Systemic therapy

Review articles
Male Breast Cancer: Prognostic Factors

- Nodal status
- Age
- Tumor size
- ER / PR Expression
- Ki-67 Expression
- Grade
- Genomic signatures

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<td>Tumor size</td>
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<tr>
<td>ER / PR Expression</td>
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<td>Ki-67 Expression</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
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<tr>
<td>Grade</td>
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<tr>
<td>Genomic signatures</td>
<td>2b</td>
<td>B</td>
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</tbody>
</table>

Registries
Male Breast Cancer: Systemic Therapy

- (Neo-)adjuvant chemotherapy as in women
  - HER2-targeted therapy (if HER2-positive)
  - Endocrine therapy
    - Tamoxifen
    - GnRHa and AI
    - Aromatase inhibitors without GnRHa
    - Fulvestrant (metastatic BC)
    - CDK4/6i (in combination)
  - Palliative chemotherapy as in women

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>(Neo-)adjuvant</td>
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<tr>
<td>chemotherapy as in</td>
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<td>women</td>
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<tr>
<td>HER2-targeted</td>
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<tr>
<td>therapy (if HER2-positive)</td>
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<td>Endocrine therapy</td>
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<td>++</td>
</tr>
<tr>
<td>Tamoxifen</td>
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<td>++</td>
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<td>GnRHa and AI</td>
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<td>Aromatase inhibitors</td>
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<tr>
<td>without GnRHa</td>
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<td>Fulvestrant (metastatic BC)</td>
<td>4</td>
<td>+/-</td>
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<td>CDK4/6i (in combination)</td>
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<td>Palliative</td>
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<td>chemotherapy as in</td>
<td></td>
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<tr>
<td>women</td>
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</tr>
</tbody>
</table>

Statement: Adjuvant Chemotherapy

Statement Trastuzumab

Statement CDK4/6i

Statement endocrine therapy

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


8. van Uden DJ, Breveld R, Siesling S et al. Inflammatory breast cancer in the Netherlands; improved survival over the last decades.

### Inflammatory Breast Cancer (IBC, cT4d)

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>AGO</th>
<th>General Management</th>
</tr>
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<tr>
<td>2c</td>
<td>B</td>
<td>Staging (including adequate breast imaging) ++</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Skin punch biopsy (at least 2; detection rate &lt; 75%) +</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC) ++</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Mastectomy after chemotherapy +</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Breast conserving therapy in case of pCR (individual) +/-</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Delayed breast reconstruction +</td>
</tr>
<tr>
<td>3b</td>
<td>C</td>
<td>Sentinel excision only -</td>
</tr>
<tr>
<td>2c</td>
<td>B</td>
<td>Radiotherapy of the chest wall including regional lymph nodes independent of therapy response ++</td>
</tr>
</tbody>
</table>

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


Survival benefit by trimodal treatment (NACT, MRM, RT)


Statement: Staging


Statement: Regimens as in non-inflammatory BC


Statement: Mastectomy after chemotherapy

4. Tsai CJ et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed

Statement: Immediate breast reconstruction:

Statement: Sentinel lymph node

Statement: Radiotherapy
Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Diagnostic Imaging

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<tr>
<td>Breast imaging incl. Breast-MRI</td>
<td>3</td>
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<td>++</td>
</tr>
<tr>
<td>Exclude contralateral cancer</td>
<td>3</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Staging (CT thorax / abdomen, pelvis, bone scan)</td>
<td>3</td>
<td>B</td>
<td>++</td>
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<tr>
<td>If histological diagnosis is not certain</td>
<td>5</td>
<td>D</td>
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</tr>
<tr>
<td>Exclude non-breast malignancy, especially in case of TNBC (e.g. NEC, female genital tract, lung, thyroid gland, stomach, skin, ENT)</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

Statement: Mammography / Breast ultrasound / Breast MRI

Statement: Staging

Statement: PET
Guidelines


Reviews


Pathology

Outcome


**Axillary Metastasis in Occult Breast Cancer (ex. CUP)**

Pathology, Molecular Pathology

<table>
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<td>Immunohistochemistry (ER, PR, HER2, Ki-67, GATA)</td>
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<td>D</td>
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<tr>
<td>Immunohistochemistry (e.g. Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, Synaptophysin etc.) to exclude other primary malignancies in case of TNBC phenotype or unusual histology, e.g. NEC, female genital tract, lung, ENT tumors, thyroid, stomach, skin</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)</td>
<td>2c</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPICup)</td>
<td>2c</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Prognostic gene expression tests</td>
<td>5</td>
<td>D</td>
<td>--</td>
</tr>
</tbody>
</table>

---

**Immunohistochemistry**

Gene expression profiling and other molecular approaches in CUP disease


Axillary Metastasis in Occult Breast Cancer (Axillary CUP): Therapy

Guidelines


Reviews


Statement: Axillary dissection


Statement TALD + RT nach NACT

Statement: Mastectomy without (in-)breast tumor

Statement: Breast irradiation if breast MRI is negative
2. Kim H, Park W, Kim SS et al. Prognosis of patients with axillary lymph node metastases from occult breast cancer: analysis of


**Statement: Systemic treatment according N+ tumor**


Paget’s Disease of the Breast Diagnosis

“Mammary Paget Disease is a Sentinel Sign”

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Histological verification by skin biopsy*</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography, sonography</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>MRI of the breast if other imaging negative</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Immunohistochemistry (ER, PR, HER2, CK7) to detect benign and HER2-negative cases</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

* including all skin strata (e.g. by punch biopsy or wedge excision)

General recommendations / Guidelines:

Imaging
Pathology
Paget’s Disease of the Breast

- Definition: Paget’s disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer.
- Clinical presentation: skin eczema of the nipple, areola and surrounding skin; thickening, pigmentation and scaly skin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Paget’s disease with invasive Ca. (37-58%)</td>
</tr>
<tr>
<td></td>
<td>Paget’s disease mit DCIS (30-63%)</td>
</tr>
<tr>
<td></td>
<td>Isolated Paget’s disease (4-7%)</td>
</tr>
<tr>
<td></td>
<td>Isolated Paget’s disease with invasion (rare)</td>
</tr>
<tr>
<td>IHC</td>
<td>HER2-positive (83-97%)</td>
</tr>
<tr>
<td></td>
<td>ER-positive (10-14%)</td>
</tr>
<tr>
<td></td>
<td>AR-positive (71-88%)</td>
</tr>
<tr>
<td>Prognosis and tumor biology</td>
<td>Better in isolated Paget’s disease</td>
</tr>
<tr>
<td></td>
<td>Worse if in combination with invasive breast cancer or DCIS compared to isolated Paget’s disease</td>
</tr>
</tbody>
</table>

Review

Clinical Presentation
Pathology and Immunohistochemistry
## Paget’s Disease of the Breast Therapy

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paget’s disease with underlying disease (invasive breast cancer, DCIS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Therapy according to standard of underlying disease</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>• Surgery must achieve R0</td>
<td>1c</td>
<td>B</td>
</tr>
<tr>
<td><strong>Isolated Paget’s disease of the NAC:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Surgery must achieve R0</td>
<td>1c</td>
<td>B</td>
</tr>
<tr>
<td>• Surgical resection only, no adjuvant radiotherapy</td>
<td>4</td>
<td>D</td>
</tr>
<tr>
<td>• Sentinel-node excision (SLNE)</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

**General recommendations / Guidelines:**

**Surgical Treatment of Paget’s disease associated with breast tumor (invasive carcinoma or DCIS)**
Treatment of isolated Paget's disease


Statement: Sentinel-node excision (SNE)


Borderline and Malignant Phyllodes Tumor Diagnosis

- Mammography, sonography
- Diagnosis on core biopsy, grade determination on resection specimen
- Breast MRI
- Staging only malignant PT (CT thorax / abdomen, bone scan)

<table>
<thead>
<tr>
<th>Ottawa LoE</th>
<th>AGO</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>C</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>+/-</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>D</td>
<td>++</td>
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<td></td>
</tr>
</tbody>
</table>

Review

Imaging

Core biopsy
Borderline and Malignant Phyllodes Tumor

- Name derived from greek term of “Phyllon” (leaf) due to its lobulated histological aspect
- Differential diagnosis may be problematic on core biopsy
- Resection margin is independent prognostic parameter
- Comparable rates of recurrence in association with BCT or mastectomy
- In-Breast recurrence relatively frequently seen (10 - 30%)
- Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.
- Adverse pathological criteria: marked stromal cellularity and overgrowth, increased nuclear atypia, presence of large necrohemorrhagic areas, and high mitotic activity associated with increased risk of distant recurrence

Review

Pathology and Outcome
Phyllodes Tumor

- Frequency 0.3–1% of all primary breast tumors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading system (3-STEP histological grading</td>
<td>Benign (75%)</td>
</tr>
<tr>
<td>system)</td>
<td>Borderline (16%)</td>
</tr>
<tr>
<td></td>
<td>Malignant (9%)</td>
</tr>
<tr>
<td>Median age at time of diagnosis</td>
<td>Benign PT: 39 y</td>
</tr>
<tr>
<td></td>
<td>Borderline PT: 45 y</td>
</tr>
<tr>
<td></td>
<td>Malignant PT: 47 y</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>Benign PT: 4–17%</td>
</tr>
<tr>
<td></td>
<td>Borderline PT: 14–25%</td>
</tr>
<tr>
<td></td>
<td>Malignant PT: 23–30%</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Benign PT: &lt; 1%</td>
</tr>
<tr>
<td></td>
<td>Borderline: PT: 1.6%</td>
</tr>
<tr>
<td></td>
<td>Malignant PT: 16–22%</td>
</tr>
</tbody>
</table>

10 y OS: 86–90% (range: 57–100%) depending on subtype and unfavorable histological criteria

Review

Pathology and Outcome
Borderline and Malignant Phyllodes Tumor Surgery

- Fibroepithelial lesions with rapid growth or size > 3 cm should be excised (independently from the any CNB result)
  - Oxford LoE 5 D ++
- If the result of the CNB is unclear or suspicious for PT, excision with clear margins should be performed
  - Oxford LoE 5 D ++
- SLNE / Axillary dissection (if clinically unsuspicious)
  - Oxford LoE 4 C --
- Treatment of local recurrence
  - R0 resection or simple mastectomy
  - Oxford LoE 4 C ++

General recommendations / Guidelines:
**Surgical margins: Observational study:**

**Surgical margins: Systematic review**

**Operative management and prognosis of Phyllodes Tumors**
Statement: SNE / Axillary dissection in cN0

Statement: Staging
Borderline and Malignant Phyllodes Tumor - Margins -

- Intended lesion-free surgical margins are*
  - in borderline PT: ≥ 2 mm
  - in malignant PT: ≥ 10 mm

- Intended pathologically lesion-free margins are*
  - in borderline PT: negative ("no ink on the tumor")
  - in malignant PT: ≥ 2 mm

- Re-resection recommended
  - in borderline PT: if margin* positive ("tumor on ink")
  - in malignant PT: if margin < 2 mm

* Margins related to breast tissue only (but not to skin or to the thoracic wall)

General recommendations / Guidelines:

Surgical margins: Observational study:

Surgical margins: Systematic review


Operative management and prognosis of Phyllodes Tumors


Statement: SNE / Axillary dissection in cN0

Statement: Staging
Borderline and Malignant Phyllodes Tumor
- Adjuvant Radiotherapy -

Adjuvant radiotherapy of the breast and the thoracic wall is aimed at local control.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Oxford LoE</th>
<th>Oxford GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCS, R0-resection</strong></td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>- Borderline PT: no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Malignant PT: yes (independently from the size of the lesion)</td>
<td></td>
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</tr>
<tr>
<td><strong>Mastectomy, R0-resection</strong></td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>- Borderline PT: no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Malignant PT: &lt; 5 cm: no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Malignant PT: ≥ 5 cm: with aggressive pathology or growth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mastectomy, R1-resection</strong></td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>- Borderline PT: no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Malignant PT: ja (independently from the size of the lesion)</td>
<td></td>
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</tr>
</tbody>
</table>

General recommendations / Guidelines:
Surgical margins: Systematic review


Operative management and prognosis of Phyllodes Tumors


Statement: SNE / Axillary dissection in cN0


Statement: Staging


General recommendations / Guidelines:

**Statements: Systemic adjuvant therapy/ Chemotherapy and Endocrine therapy**


**Statement: Adjuvant radiotherapy**


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

**Statement:** Distant metastases (very rare) => Treatment like soft tissue sarcomas

Primary Angiosarcoma of the Breast*
Diagnosis

- Mammography, sonography to determine extent of disease
- Preoperative MRI to determine the extent of disease
- Diagnosis by core biopsy
- Diagnosis by FNB
- Staging (CT thorax & abd.; angiosarcoma: MRI brain)
- Prognostic factors: size, grade, margins

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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<tbody>
<tr>
<td></td>
<td>3a</td>
<td>C</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>C</td>
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<tr>
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<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>

* Therapy in specialized centers recommended

Review

Imaging

Pathology


**Prognostic Factors**


Sarcomas of the Breast

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

10. Kunkiel, M., Maczkiewicz
Primary Angiosarcoma of the Breast

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

Reviews
Sep;28(9):5112-5118.
Primary Angiosarcoma of the Breast*

Therapy

- Surgery with wide clear margins, mostly as mastectomy
  - Breast-conserving therapy
  - SLNE or axillary dissection if cN0
- Adjuvant chemotherapy (anthracycline / taxane-based)
- Adjuvant radiotherapy if high risk (size > 5 cm, R1)

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

*Therapy in specialized centres recommended

Reviews


Surgery

Adjuvant Treatment (Chemotherapy, Radiotherapy)

## Secondary Angiosarcoma of the Breast Therapy

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

- **Tumor resection (BCT / mastectomy)**
  - Radical surgery is not associated with better outcome
- **(Neo-)adjuvant chemotherapy**
  - Consider „trimodality treatment“ in case of locally advanced angiosarcoma (neoadjuvant taxanes => neoadjuvant radiochemotherapy => surgical resection)  
    | 3a | C | + |
- **Adjuvant radiotherapy if high risk**
  - (size > 5 cm, R1)  
    | 2b | B | +/- |
- **Regional hyperthermia (to improve local control)**
  - plus chemotherapy and / or radiotherapy  
    | 2b | B | +/- |

### Review


### Surgery (BEO/mastectomy)


(Neo-)Adjuvant Chemotherapy

Trimodale Therapie (Mayo)

Adjuvant Radiotherapy

Adjuvant Hyperthermia
Trimodality Therapy Improves Disease Control in Radiation-Associated Angiosarcoma of the Breast (RAASB)

38 patients (median age 69 years) with RAASB; median F/U 5,6 y

- **Trimodality therapy** consisted of
  1. taxane induction therapy, followed by
  2. concurrent taxane and irradiation therapy, followed by
  3. surgical resection with wide margins.

**Results:**

- **n = 16 trimodal therapy:** pCR 12/16
  
<table>
<thead>
<tr>
<th>Loc.rec.</th>
<th>dist.met.</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/16</td>
<td>1/16</td>
<td>1/16</td>
</tr>
</tbody>
</table>

  
- **Wound break / sec. wound-healing:** 100%

- **n = 22 monotherapy/dual therapy:**
  
<table>
<thead>
<tr>
<th>Loc.rec.</th>
<th>dist.met.</th>
<th>death</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/22</td>
<td>8/22</td>
<td>7/22</td>
</tr>
</tbody>
</table>

  
- **Wound break / sec. wound-healing:** 48% (p < 0.001)

- **RFS; 93.8% vs. 42.9%; P = 0.004; HR, 7.6 (95% CI: 1.3-44.2)**


**Trimodality Therapy (Mayo)**

Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years
- Clinical presentation
  - > 5 years after BCT or mastectomy with irradiation
  - usually intracutaneously or subcutaneously in the irradiation area with livid discoloration
  - multiple foci
  - most often in advanced stages (II - III)
  - metastasis mostly pulmonary
  - lymph node metastasis possible
- Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma
- Survival: after 5 yrs. up to 50.5%, after 10 yrs. up to 25.2%

Review

Radiotherapy


## Angiosarcoma of the Breast
### Treatment of Local Recurrence and Metastases

<table>
<thead>
<tr>
<th>Treatment of Local Recurrence:</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant radiotherapy for high-risk patients (tumor size &gt; 5 cm, R1)</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

### Distant Metastases / Unresectable Tumors:

- Treatment like as for soft tissue sarcomas (according to S3 guideline) | 4          | C  | ++  |
- Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma) | 2b         | B  | +   |
- Antiangiogenic treatment (e.g. in angiosarcoma) | 4          | C  | +/- |

### If clinically resistant to therapy

- Molecular diagnostics (Multidisciplinary molecular board) | 5          | D  | +   |

---

### Review


### Treatment of local recurrences


### Treatment of metastatic and non-resectable tumors


Molecular Diagnostics if clinically resistant to therapy
Therapy review:

Surgery

Axilla

Adjuvant chemotherapy

Neoadjuvant chemotherapy

Adjuvant endocrine therapy

Adjuvant radiotherapy
**Metaplastic Breast Carcinoma – Low Grade With Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical therapy and axillary staging as in case of NST</td>
<td>4</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Adjuvant chemotherapy (frequently chemoresistant)</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy (frequently chemoresistant)</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Adjuvant endocrine therapy (not applicable, since triple-negative tumors)</td>
<td>4</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Adjuvant radiotherapy according therapy of NST</td>
<td>4</td>
<td>C</td>
<td>+</td>
</tr>
</tbody>
</table>

* Reference pathology recommended

**Review**


**Fibromatose-ähnliches Mammakarzinom (low-grade)**


Adenosquamöses metaplastisches Karzinom (low grade)


**Metaplastic Breast Cancer**

**Definition:**
Metaplastic transformation of epithelial tumor cells

- Epithelial differentiation: squamous cell carcinoma, spindle-cell carcinoma
- Heterologous (mesenchymal) differentiation: chondroid, osseous or otherwise metaplastic breast cancer

**Clinical and pathological characteristics:**
- < 1 % of malignant breast neoplasms
- Similar age group as NST breast cancer
- Localized, mostly palpable
- Rapidly growing, poor response to chemotherapy
- > 90 % triple-negative

**Subtypes:**
- Highly aggressive with squamous cell or high-grade spindle-cell differentiation
- Less aggressive (low-grade) with mesenchymal, low grade adenosquamous or fibromatosis-like differentiation

**Frequent mutations:**
- TP53, EGFR, PIK3CA, PTEN
- Possible association to BRCA1-mutation/HRD-positivity

**Background**

Outcome


Molecular features

