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
Breast Cancer: Specific Situations

- **Versions 2005–2022:**
  - Dall / Ditsch / Fehm / Fersis / Friedrich / Gerber / Gluz / Göhring / Harbeck / Huober / Janni / Kolberg-Liedtke / Loibl / Lück / Lux / Maass / Mundhenke / Müller / Oberhoff / Rody / Scharl / Schneeweiss / Schütz / Sinn / Solomayer / Stickeler / Thomssen

- **Version 2023**
  - Mundhenke / Schmidt

**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
Breast Cancer:
Specific Situations

- Young patients
- Pregnancy- and breast-feeding-associated BC
- Elderly patients
- Male patients
- Inflammatory BC
- Occult Breast Cancer (Cancer of unknown primary – axillary CUP)
- Paget’s disease
- Malignant and Borderline Phyllodes Tumor
- Angiosarcoma
- Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)
- Metaplastic breast cancer
Breast Cancer in Young Women ≤ 40 Years


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)


9. Moore HCF, Unger JM, Phillips KA, et al Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance). J Clin Oncol 32:5s, 2014 (suppl; abstr LBA505)

Surgery in young women (Surgery like ≥ 35y - in particular BCT)


Genetic and fertility counselling


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)


**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*
– Delivery and Breast-Feeding –

**General principles**

**Statements:**
- Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)
- Termination of pregnancy does not improve maternal outcome
- Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir
- If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities

*Participation in register study recommended

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tbody>
<tr>
<td>Delivery should be postponed until sufficient fetal maturation (avoid iatrogenic prematurity)</td>
<td>2b</td>
<td>C</td>
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<tr>
<td>Termination of pregnancy does not improve maternal outcome</td>
<td>3b</td>
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<tr>
<td>Delivery mode like in healthy women; avoid delivery during chemotherapy-induced leucocyte nadir</td>
<td>4</td>
<td>C</td>
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<tr>
<td>If further systemic therapy is needed after delivery, breast feeding may be contra-indicated depending on drug toxicities</td>
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</tr>
</tbody>
</table>

*Participation in register study recommended

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**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
### General principles


### Statement

Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adequately.

### Breast Cancer During Pregnancy and Lactation*  
- Outcome -

<table>
<thead>
<tr>
<th>Oxford LoE</th>
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<tbody>
<tr>
<td>BC during pregnancy</td>
</tr>
<tr>
<td>- Prognosis is not worse if adequately treated 3a</td>
</tr>
<tr>
<td>BC during lactation and within the first year after pregnancy</td>
</tr>
<tr>
<td>- Prognosis worse than in BCP and if unrelated to pregnancy 3a</td>
</tr>
<tr>
<td>Pregnancy / lactation after BC</td>
</tr>
<tr>
<td>- Outcome not compromised 3a</td>
</tr>
</tbody>
</table>

* Participation in register study recommended
Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

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


Review articles


Geriatric Assessment

- No specific algorithm is available
- Ability to tolerate treatment varies greatly ("functional reserve")
- Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services
- Assessment tools:
  - Charlson Comorbidity Index (widely used; good predictor over a 10-year period)
  - 12 prognostic indicators to estimate 4-year mortality risk
  - Short screening tests (more qualitative evaluation)
  - IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8
  - Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)

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

- Clinical geriatric assessment
  - Treatment according to guidelines
    - Surgery similar to “younger” age
    - Endocrine treatment (endocrine responsive)
    - Chemotherapy (standard regimen)
      - < 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

Oxford

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</tbody>
</table>

* 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)

**Options extrapolated from trials in elderly:**

- No breast surgery (consider endocrine options)
- 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

**Reduced standard treatment**

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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

**Diagnosis Work-Up as in Women**
- Ultrasound
- Mammography

**Standard-Surgery: Mastectomy**
- BCT is an option (tumor / breast relation)
- Sentinel-node excision (SLNE)

**Radiotherapy as in women**
(consider tumor / breast relation)

**Genetic counseling if one additional relative affected**
(breast / ovarian cancer)

**Screening for 2nd malignancies according to guidelines**

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<tr>
<td>Ultrasound</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Mammography</td>
<td>3b</td>
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<td>Breast Cancer in Men: Diagnostic Work-Up and Loco-Regional Therapy</td>
<td>4</td>
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<tr>
<td>BCT is an option (tumor / breast relation)</td>
<td>4</td>
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<tr>
<td>Sentinel-node excision (SLNE)</td>
<td>2b</td>
<td>B</td>
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</tr>
<tr>
<td>Genetic counseling if one additional relative affected (breast / ovarian cancer)</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>Screening for 2nd malignancies according to guidelines</td>
<td>GCP</td>
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</tbody>
</table>

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

---

**International Registry**

**General**

Statement: Diagnostic work up as in women

Statement: Mammography

Statement: Ultrasound

Statement: Standard-surgery: Mastectomy – men

Statement: Sentinel-node excision (SNE)
2. Flynn LW et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg. 2008 Apr;206(4):616-

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

<table>
<thead>
<tr>
<th>Oxford</th>
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<td>Nodal status</td>
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<tr>
<td>Age</td>
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<tr>
<td>Tumor size</td>
<td>2b</td>
<td>A</td>
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<tr>
<td>ER/PR Expression</td>
<td>2b</td>
<td>A</td>
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<tr>
<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 (e.g. OncotypeDx)</td>
<td>2b</td>
<td>B</td>
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## 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

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</tr>
</tbody>
</table>

Statement: Adjuvant Chemotherapy

Statement: Trastuzumab

Statement CDK4/6i

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
Inflammatory Breast Cancer (IBC, cT4d)

<table>
<thead>
<tr>
<th>Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d</th>
<th>Oxford</th>
</tr>
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<tbody>
<tr>
<td>2c B ++</td>
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</table>

- **Staging**
  - Skin punch biopsy (at least 2; detection rate < 75%)
  - Treatment according to guidelines (neoadjuvant or adjuvant – as in non-IBC)
  - Mastectomy after chemotherapy
    - Breast conserving therapy in case of pCR (individual)
    - Delayed breast reconstruction
    - Sentinel excision only
  - Radiotherapy of the chest wall including regional lymph nodes independent of therapy response

**General**

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

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 (Cancer of Unknown Primary – Axillary CUP)

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

Guidelines


Reviews


Pathology

Outcome
Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Imaging Diagnostics

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Breast imaging incl. Breast-MRI</strong></td>
<td>3</td>
<td>B</td>
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<tr>
<td><strong>Exclude contralateral cancer</strong></td>
<td>3</td>
<td>B</td>
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<tr>
<td><strong>Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)</strong></td>
<td>5</td>
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<tr>
<td><strong>Staging</strong> (CT thorax / abdomen, pelvis, in certain circumstances also thyroid sonography, HNT-exam)</td>
<td>3</td>
<td>B</td>
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<tr>
<td><strong>PET / PET-CT</strong></td>
<td>3b</td>
<td>B</td>
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</tbody>
</table>

Statement: Mammography / Breast ultrasound/ Breast MRI


Statement: Staging


Statement: PET


Axillary Metastasis in Occult Breast Cancer (ex. CUP)
Pathology, Molecular Pathology

- ER, PR, HER2, GATA3 (in some cases Ck5/6, Ck7, Ck20, SOX-10, PAX-8, TTF1, and others)
- Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.
- Gene expression profiling for determination or primary site (e.g. CUPprint, Pathwork, TOT, CancerType)
- NGS, epigenetics for determination of primary site (Panel-Sequencing, e.g. EPIcUp)
- Prognostic gene expression tests

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Immunohistochemistry


Gene expression profiling and other molecular approaches in CUP disease


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

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<th>Oxford</th>
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<tbody>
<tr>
<td>Axillary dissection</td>
<td>3a</td>
<td>C</td>
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</tr>
<tr>
<td>Targeted axillary dissection after NACT (in case of clinical complete remission)</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
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<tr>
<td>Mastectomy if breast MRI is negative</td>
<td>3a</td>
<td>C</td>
<td>--</td>
</tr>
<tr>
<td>(Neo-)adjuvant systemic therapy according to breast cancer guidelines (AGO)</td>
<td>5</td>
<td>D</td>
<td>++</td>
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<tr>
<td>Breast irradiation if breast MRI is negative</td>
<td>2c</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)</td>
<td>3b</td>
<td>B</td>
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</table>

Guidelines


Reviews


Statement: Axillary dissection


**Statement: Mastectomy without (in-)breast tumor**


**Statement: Breast irradiation if breast MRI is negative**


Does it Reduce the Local Recurrence Rate and Increase Overall Survival? Clinical Oncology (Royal College of Radiologists (Great Britain)), 23(2), 95–100. http://doi.org/10.1016/j.clon.2010.10.001


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


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


Clinical Presentation


Pathology and Immunohistochemistry


Paget’s Disease of the Breast Diagnosis

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

General recommendations / Guidelines:


Imaging

Pathology


Paget’s Disease of the Breast - Therapy

- 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

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

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

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**Review**


**Pathology and Outcome**


Borderline and Malignant Phyllodes Tumor Diagnosis

<table>
<thead>
<tr>
<th>Oxford</th>
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</thead>
<tbody>
<tr>
<td>Mammography, sonography</td>
<td>3</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Diagnosis on core biopsy, grade determination on resection specimen</td>
<td>3</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>3</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Staging only malignant PT (CT thorax, skeletal system)</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

Imaging


Core biopsy


Borderline and Malignant Phyllodes Tumor Surgery

General recommendations / Guidelines:

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 Therapy

- Adjuvant radiotherapy (younger age, increased tumor volume > 5 cm, close resection margin)
  - Local control
  - Effect on disease-free survival
- Systemic adjuvant therapy (chemo, endocrine)
- Adjuvant Treatment of local recurrence
  - Radiotherapy, chemotherapy after R1 resection
- Distant metastasis (very rare)
  - Treatment like soft tissue sarcomas

<table>
<thead>
<tr>
<th></th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LoE</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>2b</td>
</tr>
<tr>
<td>Systemic adjuvant therapy</td>
<td>4</td>
</tr>
<tr>
<td>Adjuvant Treatment of local recurrence</td>
<td>4</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>4</td>
</tr>
</tbody>
</table>

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


Clinical Oncology, 30(6), 570–573. http://doi.org/10.1097/COC.0b013e3181131d62
9. 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

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

Oxford LoE GR AGO
3a C ++
3a C ++
3a C --
4 D ++

* Therapy in specialized centers recommended

Imaging


Pathology


Prognostic Factors


Primary Angiosarcoma of the Breast*

Therapy

Surgery


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Adjuvant Treatment (Chemotherapy, Radiotherapy)

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* Therapy in specialized centres recommended


### Secondary Angiosarcoma of the Breast Therapy

#### Surgery (BEO/mastectomy)


#### (Neo-)Adjuvant Chemotherapy


<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor resection (BCT / mastectomy)</strong></td>
<td>3a</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Radical surgery is not associated with better outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Neo-)adjuvant chemotherapy</td>
<td>3a</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Adjuvant radiotherapy if high risk</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>(size &gt; 5 cm, R1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional hyperthermia (to improve local control) plus chemotherapy and / or radiotherapy</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>


Adjuvant Radiotherapy


**Adjuvant Hyperthermia**


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%


Angiosarcoma of the Breast
Treatment of Local Recurrence and Metastases

### Treatment of Local Recurrence:

- R0 resection
- Adjuvant radiotherapy for high-risk patients (tumor size > 5 cm, R1)

### Distant Metastases / Unresectable Tumors:

- Treatment like as for soft tissue sarcomas (according to S3 guideline)
- Paclitaxel weekly / liposomal doxorubicin (as in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

---

**Treatment of local recurrences**


3. [https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Adulte_Weichgewebesarkome/LL_Weichgewebesarkome_Langversion_1.0.pdf](https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Adulte_Weichgewebesarkome/LL_Weichgewebesarkome_Langversion_1.0.pdf)

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**Treatment of metastatic and non-resectable tumors**


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

- Aproximately 10.000.000 implant carrier
- Rare disease, 3% of T-cell Non-Hodgkin Lymphomas, 0.04-0.5% of all malignant breast diseases
- 1:3.000 – 30.000 in women with textured implants (caveat: underreporting!)
- Estimated incidence 0.6-1.2/100.000 women with implants (median age: 54 y)
- Mainly associated with textured implants (1:300 women)
- Interval to diagnosis: 8 years (median)
- Clinical symptoms
  - Erythema, swelling and seroma. (60%)
  - Solid tumor (17%)
  - Seroma and solid tumor (20%)
  - Axillary lymphadenopathy (20%)
- Histology: CD30+ / ALK-T-Cell Lymphoma
- Compulsory registration as SAE (§ 3 MPSV to BfArM)
  (https://www.bfarm.de/SharedDocs/Formulare/DE/Medizinprodukte/BIA-ALCL-Meldung.html)

Reviews

7. BfArm recommendations
   https://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/Brustimplantate_ALCL_FDA.html (access 30.01.2021)


BIA-ALCL—Diagnosis

- Breast US (assessment of new seromas > 1 year after implant insert, solid lesion (sensitivity: 84%, specificity: 75%))
- Mamma-MRT in confirmed cases
- Staging (Imaging, e.g. CT, PET-CT)
- Cytology of late seromas
  - > 50 ml
  - Complete assessment
  - Flow-cytology (T-cell clone)
  - BIA-ALCL specific cytologic diagnostic (e.g. CD 30+)
- Core needle biopsy in solid lesions
- Lymphoma assessment of resected tissue and histologic staging
- Documentation of the implant and enter in registry

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>D</td>
<td>++</td>
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<tr>
<td>3a</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

BIA-ALCL—Work-up
### BIA-ALCL – Therapy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant resection and complete capsulectomy including tumorectomy</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>Contralateral implant resection including capsulectomy in case of bilateral implants (2-4% BIA-ALCL bilateral)</td>
<td>4</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Resection of suspicious lymph nodes, no routine use of Sentinel-Node-Biopsy, no axillarx dissection</td>
<td>4</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td>Systemic therapy in cases of extra capsular extension</td>
<td>4</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>Radiotherapy in unresectable tumors</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>Case discussion in an interdisciplinary tumor board in the presence of a specialist for lymphomas</td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
</tbody>
</table>

### BIA-ALCL-Treatment:


9. Brentuximab Vedotin (Neubewertung, sALCL) DGHO Stellungnahme 20211022.pdf


---

**TNM Staging of BIA-ALCL (proposed)**

<table>
<thead>
<tr>
<th>Tumor extent (cT/pT)</th>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>IA</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>T2</td>
<td>TB</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>T3</td>
<td>TC</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>T4</td>
<td>IIA</td>
<td>T4 N0 M0</td>
</tr>
<tr>
<td>Regional lymph nodes (cN/pN)</td>
<td>IIIB</td>
<td>T1-3 N1 M0</td>
</tr>
<tr>
<td>N0</td>
<td>III</td>
<td>T4 N1-2 M0</td>
</tr>
<tr>
<td>N1</td>
<td>IV</td>
<td>T any N any M1</td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis (cM/pM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TNM Kategorie**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confined to seroma or a layer on luminal side of capsule</td>
</tr>
<tr>
<td>Early capsule infiltration</td>
</tr>
<tr>
<td>Cell aggregates or sheets infiltrating the capsule</td>
</tr>
<tr>
<td>Lymphoma infiltrates beyond the capsule</td>
</tr>
<tr>
<td>No lymph node involvement</td>
</tr>
<tr>
<td>One regional lymph node positive</td>
</tr>
<tr>
<td>Multiple regional lymph nodes positive</td>
</tr>
<tr>
<td>No distant spread</td>
</tr>
<tr>
<td>Spread to other organs or distant sites</td>
</tr>
</tbody>
</table>


1. Cardoso MJ et al EUSOMA position regarding breast implant associated anaplastic large cell lymphoma (BIA-ALCL) and the use of textured implants.

BIA-ALCL – EUSOMA-Recommendation

- Despite an increase of BIA-ALCL in association with texture implants the use of textured implants is still permitted!

„For the moment, textured implants can safely continue to be used with patient’s fully informed consent, and that women that have these type of implants already in place don’t need to remove or substitute them, which would undoubtedly cause harm to many tens of thousands of women, to prevent an exceptionally rare, largely curable and currently poorly understood disease.”
Background


and comparison with other invasive breast cancer types. Breast. 2019 Feb;43:135–141. PMID: 30553188


Outcome


Molecular features


Therapy review:


**Surgery**


Axilla

Adjuvant chemotherapy


Neoadjuvant chemotherapy


Adjuvant endocrine therapy


Adjuvant radiotherapy


Metaplastic Breast Carcinoma with Uncertain Malignant Potential (Fibromatous and Adenosquamous Ca.)*

- Operative therapy and axillary staging according to standard
  - Oxford LoE 4 C ++
- Adjuvant chemotherapy
  - Oxford LoE 4 C -
- Neoadjuvant chemotherapy
  - Oxford LoE 4 C - -
- Adjuvant endocrine therapy (not applicable, since triple-negative tumors)
  - Oxford LoE 4 C -
- Adjuvant radiotherapy according to standard
  - Oxford LoE 4 C +

* Reference pathology recommended

Fibromatose-ähnliches Mammakarzinom (low-grade)


Adenosquamoses metaplastisches Karzinom (low grade)