Breast Cancer: Specific Situations
Breast Cancer: Specific Situations

- **Versions 2005-2016:**
  Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Harbeck / Huober / Janni / Loibl / Lück / Lux / Maass / Mundhenke / Oberhoff / Rody / Scharl / Schneeweiss / Solomayer / Thomssen

- **Version 2017:**
  Schütz / Sinn
Breast Cancer: Specific Situations

- Young patients
- Pregnancy- and breast-feeding-associated BC
- Elderly patients
- Male patients
- Inflammatory BC
- Occult Breast Cancer (Cancer of unknown primary – axillary CUP)
- Paget’s disease
- Malignant and Borderline Phyllodes Tumor
- Angiosarcoma
- Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL)
Breast Cancer in Young Women ≤ 35 Years

- Aggressive biological behavior with worse prognosis
- Surgery like patients ≥ 35 y
- Guidelines adapted (neo-)adjuvant systemic treatment (see chapters there)
- GnRHa as ovarian protection (see chapter gyn. problems)
- Genetic and fertility counseling
- Contraception counseling

Oxford / AGO LoE / GR

| 2a  | B  |
| 2b  | B  | + |
| 1b  | A  | ++ |
| 1b  | B  | + |
| 2b  | B  | ++ |

++
Breast Cancer During Pregnancy* or Breast Feeding – Diagnostics and Surgery

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

Oxford / AGO LoE / GR

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

* Participation in register study recommended
Breast Cancer During Pregnancy - (Neo-)adjuvant Therapy -

- Radiation therapy during pregnancy
- (Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)
  - Anthracyclines: AC, EC
  - Taxanes
  - MTX (e.g. CMF)
  - Endocrine treatment
- HER2-neu targeted treatment
- Bisphosphonates, denosumab

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GRADE</th>
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</thead>
<tbody>
<tr>
<td>Radiation therapy during pregnancy</td>
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<tr>
<td>(Neo-)adjuvant chemotherapy only after first trimester (indication as in non-pregnant)</td>
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<td>Anthracyclines: AC, EC</td>
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<td>Taxanes</td>
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<td>MTX (e.g. CMF)</td>
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<td>Endocrine treatment</td>
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<tr>
<td>HER2-neu targeted treatment</td>
<td>4</td>
<td>D -</td>
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<tr>
<td>Bisphosphonates, denosumab</td>
<td>4</td>
<td>D -</td>
</tr>
</tbody>
</table>
Breast Cancer During Pregnancy* - Delivery and Breast-Feeding -

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

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

- Delivery mode like in healthy women, avoid delivery \( \leq 3 \) weeks from last cycle of chemotherapy
  - 4 C ++

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

* Participation in register study recommended
Breast Cancer and Pregnancy - Family Planning -

- After breast cancer diagnosis reproductive techniques can be used to induce pregnancy
  - Oxford / AGO LOE / GR: 5 D ++

- Success rates for getting pregnant and for deliver a child are lower in breast cancer patients in comparison to non-cancer patients
  - Oxford / AGO LOE / GR: 5 D ++

- Breast cancer patients of reproductive age should be offered a fertility counseling before starting any kind of treatment
  - Oxford / AGO LOE / GR: 5 D ++

- Breast cancer patients should not be advised against getting pregnant regardless of tumor‘s hormone receptor status
  - Oxford / AGO LOE / GR: 5 D ++
Pregnancy Associated Breast Cancer*: Outcome

- BC during pregnancy / lactation
  - Adequate treatment is essential

- Pregnancy and lactation after BC
  - Outcome not compromised

* Participation in register study recommended
Geriatric Assessment

- No specific algorithm is available
- Ability to tolerate treatment varies greatly („functional reserve“)
- Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services
- Assessment tools:
  - Charlson Comorbidity Index (widely used; good predictor over a 10-year period)
  - 12 prognostic indicators to estimate 4-year mortality risk
  - Short screening tests (more qualitative evaluation)
  - IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8
  - Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)
Treatment for Fit Elderly Patients
(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

- Clinical geriatric assessment
- Treatment according to guidelines
  - Surgery similar to „younger“ age
  - Endocrine treatment (endocrine resp.)
  - Chemotherapy (standard regimens)
    - < 70 years
    - > 70 years (especially N+, ER/PgR-)
  - Radiotherapy
  - Omit radiotherapy after BCT in low risk with endocrine treatment
  - Trastuzumab

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<thead>
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<th>Oxford / AGO LoE / GR</th>
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*Study participation recommended
Treatment for Frail Patients
(Life Expectancy <5 yrs, Substantial Comorbidities)

- Reduced standard treatment
  - Oxford / AGO LoE / GR: 2b C ++

- Options extrapolated from trials in elderly:
  - No breast surgery
    - (consider endocrine options)
    - Oxford / AGO LoE / GR: 2b C +
  - No axillary clearing (≥ 60 y, cN0, rec.-pos)
    - Oxford / AGO LoE / GR: 2b B +
  - No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)
    - Oxford / AGO LoE / GR: 1b B ++
  - Hypofractionated radiotherapy
    - Oxford / AGO LoE / GR: 2b B +
  - 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

- Diagnostic work-up as in women
  - Mammography
  - Ultrasound
- Standard-surgery: Mastectomy
  - BCT is an option (tumor breast relation)
  - Sentinel-node excision (SNE)
- Radiotherapy as in women
  (consider tumor breast relation!)
- Genetic counselling if one additional relative affected (breast/ovarian cancer)
- Screening for 2nd malignancies according to guidelines

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<td>+</td>
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<td>2b</td>
<td>B</td>
<td>++</td>
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</table>

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

- Adjuvant chemotherapy as in women
  - HER2-targeted therapy
  - Endocrine therapy
    - Tamoxifen
    - Aromatase inhibitors (adjuvant)
    - Aromatase inhibitors (metastatic BC)
    - GnRHa and AI (metastatic BC)
    - Fulvestrant (metastatic BC)
- Palliative chemotherapy as in women

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<tr>
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<th>LoE / GR</th>
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<td>5 D +*</td>
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<tr>
<td>4 D ++</td>
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<tr>
<td>2b B ++</td>
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<tr>
<td>2b B -*</td>
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<tr>
<td>4 C +/-</td>
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<tr>
<td>4 C +*</td>
<td></td>
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<tr>
<td>4 C +/-</td>
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<tr>
<td>4 C ++</td>
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</tbody>
</table>

*Participation in register study recommended
## Benefit from Trimodal Treatment in Inflammatory Breast Cancer

### Median survival probability

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival Probability</th>
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<tbody>
<tr>
<td>Trimodal therapy</td>
<td>72 months</td>
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<tr>
<td>Surgery alone</td>
<td>26 months</td>
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</tbody>
</table>

### Overall survival-probability (OS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>10 years-OS</th>
<th>5 years-OS</th>
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</thead>
<tbody>
<tr>
<td>Trimodal therapy</td>
<td>55.4%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Surgery &amp; chemotherapy</td>
<td>42.9%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Surgery &amp; radiotherapy</td>
<td>40.7%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>16.5%</td>
<td></td>
</tr>
</tbody>
</table>

### Multivariate analysis of OS

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

Inflammatory Breast Cancer (IBC, cT4d)

- Invasive BC and clinical signs of inflammation (e.g. ≥ 1/3 of the breast affected) determine stage cT4d
- Staging
- Skin punch biopsy (at least 2; detection rate < 75%)
- Neoadjuvant chemotherapy (regimens as in non-inflammatory BC)
- Adjuvant systemic treatment according to guidelines
- Mastectomy after chemotherapy
  - Breast conserving therapy in case of pCR (individual)
  - Sentinel excision only
- Radiotherapy (PMRT)

Oxford / AGO LOE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Level</th>
<th>Grade</th>
<th>LOE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive BC and clinical signs of inflammation</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Staging</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Skin punch biopsy (at least 2; detection rate &lt; 75%)</td>
<td>2c</td>
<td>B</td>
<td>+</td>
<td></td>
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<tr>
<td>Neoadjuvant chemotherapy (regimens as in non-inflammatory BC)</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Adjuvant systemic treatment according to guidelines</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Mastectomy after chemotherapy</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Breast conserving therapy in case of pCR (individual)</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Sentinel excision only</td>
<td>3b</td>
<td>C</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (PMRT)</td>
<td>2c</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
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 than in breast cancer with similar tumor biology and tumor stage
Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Imaging Diagnostics

- Mammography, Breast-ultrasound, Breast-MRI
- Exclude contralateral cancer
- Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)
- Staging (CT thorax / abdomen, thyroid scintigraphy, HNT-exam)
- PET / PET-CT

<table>
<thead>
<tr>
<th>Oxford / AGO LOE / GR</th>
<th>3</th>
<th>B</th>
<th>++</th>
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<tbody>
<tr>
<td>Mammography, Breast-ultrasound, Breast-MRI</td>
<td>3</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Exclude contralateral cancer</td>
<td>3</td>
<td>B</td>
<td>++</td>
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<tr>
<td>Exclude non-breast malignancy, especially in case of TNBC (e.g. skin, female genital tract, lung, thyroid gland, stomach)</td>
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<td>D</td>
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<tr>
<td>Staging (CT thorax / abdomen, thyroid scintigraphy, HNT-exam)</td>
<td>3</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>PET / PET-CT</td>
<td>3b</td>
<td>B</td>
<td>+</td>
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</tbody>
</table>
Axillary Metastasis in Occult Breast Cancer (Axillary CUP)
Pathology, Molecular Pathology

- **ER, PgR, HER2, GATA3**
  - Oxford / AGO LOE / GR: 5 D ++

- Exclusion of other primary malignancies in case of triple-negative phenotype or unusual histology, e.g. lung, female genital tract, HNT tumors, neuroendocrine ca.
  - Oxford / AGO LOE / GR: 5 D ++

- Gene expression profiling for determination or primary site (CUPprint, Pathwork, TOT, Theros CTID)
  - Oxford / AGO LOE / GR: 2c B +/-

- NGS, epigenetics for determination of primary site (Panel-Sequencing, EPICup)
  - Oxford / AGO LOE / GR: 2c B +/-

- Prognostic gene expression tests
  - Oxford / AGO LOE / GR: 5 D - -
## Axillary Metastasis in Occult Breast Cancer (Axillary CUP) Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LOE / GR</th>
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<tr>
<td><strong>Axillary dissection</strong></td>
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</tr>
<tr>
<td><strong>Mastectomy if breast MRI is negative</strong></td>
<td>3a C -</td>
</tr>
<tr>
<td><strong>(Neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO)</strong></td>
<td>5 D ++</td>
</tr>
<tr>
<td><strong>Breast irradiation if breast MRI is negative</strong></td>
<td>3b C +/-</td>
</tr>
<tr>
<td><strong>Irradiation of regional lymph nodes according to breast cancer guidelines (AGO)</strong></td>
<td>3b B +</td>
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</table>
Paget’s Disease of the Breast

- Paget’s disease of the breast is characterized by an intraepidermal tumor manifestation originating in intraductal or invasive breast cancer. Isolated Paget’s disease of the nipple is more rarely seen, and less aggressive.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
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<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>
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<td></td>
<td>AR-positive (71 - 88%)</td>
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</tbody>
</table>
# Paget’s Disease of the Breast

## Diagnosis

1. **Histological verification by skin biopsy**

2. **Mammography, sonography**

3. **MR of the breast if other imaging negative**

4. **Immunhistology (ER, PgR, HER2, Ck7)**
   - to detect benign and HER2-negative cases

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<td>4 D</td>
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<td>+</td>
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<tr>
<td>5 D</td>
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</tbody>
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**Guidelines Breast Version 2017.1**

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Paget‘s Disease of the Breast Therapy

- Paget‘s disease with underlying disease (invasive breast cancer, DCIS)
  - Therapy according to standard of the underlying disease
  - Surgery must achieve R0
- Isolated Paget‘s disease of the NAC:
  - Surgery must achieve R0
  - Surgical resection only, no adjuvant radiotherapy
  - Sentinel-node excision (SNE)

Oxford / AGO LOE / GR

- Paget‘s disease with underlying disease (invasive breast cancer, DCIS)
  - Therapy according to standard of the underlying disease: 5 D ++
  - Surgery must achieve R0: 1c B ++
- Isolated Paget‘s disease of the NAC:
  - Surgery must achieve R0: 1c B ++
  - Surgical resection only, no adjuvant radiotherapy: 4 D ++
  - Sentinel-node excision (SNE): 2b B - -
Borderline and Malignant Phyllodes Tumor

- Differential diagnosis may be problematic on core biopsy
- In-Breast recurrence relatively frequently seen (10 - 30%)
- Distant metastasis relatively rare (< 10%) and almost exclusively seen in malignant phyllodes tumor.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Grading</td>
<td>Benign PT (75%)</td>
</tr>
<tr>
<td></td>
<td>Borderline PT (16%)</td>
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<td></td>
<td>Malignant PT (9%)</td>
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<tr>
<td>Median age on diagnosis</td>
<td>Benign PT: 39 J.</td>
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<tr>
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<td>Borderline PT: 45 J.</td>
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<tr>
<td></td>
<td>Malignant PT: 47 J.</td>
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<tr>
<td>Local recurrence</td>
<td>Benign PT: 10 - 17%</td>
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<tr>
<td></td>
<td>Borderline PT: 14 - 25%</td>
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<tr>
<td></td>
<td>Malignant PT: 23 - 30%</td>
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</tbody>
</table>
Borderline and Malignant Phyllodes Tumor Diagnosis

- Mammography, sonography
  - Oxford / AGO LOE / GR: 3 C ++
- Diagnosis on core biopsy, grading on resection specimen
  - Oxford / AGO LOE / GR: 3 C ++
- Breast MRI
  - Oxford / AGO LOE / GR: 3 C +/-
- Staging only malignant PT (CT thorax, skeletal system)
  - Oxford / AGO LOE / GR: 5 D ++
Borderline and Malignant Phyllodes Tumor Surgery

- **R0-Excision**
- **SNE / Axillary dissection when cN0**
- **Treatment of local recurrence**
  - R0 resection or simple mastectomy

**Oxford / AGO LOE / GR**

- R0-Excision: 2b B ++
- SNE / Axillary dissection when cN0: 4 C -
- Treatment of local recurrence: 4 C ++
Borderline and Malignant Phyllodes Tumor
Adjuvant Therapy

- Adjuvant radiotherapy
  - If $T \geq 2$ cm (BCT) or $T \geq 10$ cm (mastectomy)
  - Systemic adjuvant therapy (chemo, endocrine)
- Treatment of local recurrence
  - R0 resection or simple mastectomy
  - Radiotherapy, chemotherapy after R1 resection
- Distant metastases (very rare)
  - Treatment like soft tissue sarcomas

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<td>C</td>
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Sarcomas of the Breast

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

- Most common primary sarcoma of the breast
- Young age (median: 24 - 46 years)
- Indistinct tumor borders
- Large tumor (median: 5 - 7 cm)
- Uncharacteristic findings on mammography and sonography
- High local recurrence risk, even after mastectomy
- More unfavorable prognosis than other primary sarcoma of the breast
Primary Angiosarcoma of the Breast*

**Diagnosis**

- Mammography, sonography to determine extent of disease
  - Oxford / AGO
  - LOE / GR
  - 3a C --

- Preoperative MRI to determine the extent of disease
  - Oxford / AGO
  - LOE / GR
  - 3a C ++

- Diagnosis by core biopsy
  - Oxford / AGO
  - LOE / GR
  - 3a C ++

- Diagnosis by FNB
  - Oxford / AGO
  - LOE / GR
  - 3a C --

- Staging (CT thorax & abd.; angiosarcoma: MRI brain)
  - Oxford / AGO
  - LOE / GR
  - 4 D ++

- Prognostic factors: size, grade, margins
  - Oxford / AGO
  - LOE / GR
  - 3a C ++

*Therapy in specialized centres recommended*
Primary Angiosarcoma of the Breast*

Therapy

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

Oxford / AGO
LOE / GR

3a C ++
3a C -
3a C - -
4 C +/-
4 C +/-

* Therapy in specialized centres recommended
Secondary (Radiotherapy-associated) Angiosarcoma of the Breast

- Cumulative incidence of radiotherapy-associated sarcoma: 3.2 per 1,000 after 15 years

- Clinical presentation
  - > 5 years after BCT or mastectomy with irradiation
  - usually intracutaneously or subcutaneously in the irradiation area with livid discoloration
  - multiple foci
  - most often in advanced stages (II - III)
  - metastases mostly pulmonary
  - lymph node metastasis possible

- Prognosis is more unfavorable than in non-radiotherapy-associated sarcoma

- Survival after 5 years: 15%
### Secondary Angiosarcoma of the Breast

**Therapy**

- **Secondary mastectomy**
  - *Oxford / AGO LOE / GR*: 3a C ++

- **Adjuvant chemotherapy** (anthracycline/taxane-based)
  - *Oxford / AGO LOE / GR*: 2b B +/-

- **Adjuvant radiotherapy if high risk** (size > 5 cm, R1)
  - *Oxford / AGO LOE / GR*: 2b B +/-

- **Regional hyperthermia (to improve local control) plus chemotherapy and/or radiotherapy**
  - *Oxford / AGO LOE / GR*: 2b B +/-
Angiosarcoma of the Breast

Treatment of Local Recurrence and Metastases

Treatment of Local Recurrence:
- R0 resection
- Radiotherapy, chemotherapy after R1 resection

Distant Metastases / Unresectable Tumors:
- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)

Oxford / AGO LOE / GR

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

- Rare, estimated annual incidence <1 per 100,000 women with implants (median age 54 years)
- Occurrence predominantly of textured implants
- 5-year OAS 89%
- Interval for lymphoma diagnosis: 8 years (median)
- Clinical presentation
  - Effusion only (60%)
  - Mass only (17%)
  - Effusion and mass (20%)
- Histological: CD30 + / ALK-T cell lymphoma
- Reporting obligation as SAE according to § 3 MPSV to the BfArM
Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Diagnosis -

- Sonography (for newly occurring seromas 1 year after implant placement, tumor mass) 5 D ++
- Breast MRI on confirmation of the diagnosis 5 D ++
- Nodal status, PET-CT, bone marrow biopsy 5 D ++
- Cytology of effusion (for newly occurring seromas 1 year after implant placement) with requisition ”r/o BIA-ALCL” 5 D ++
- Lymphoma diagnosis on resection specimen and histological staging (acc. to Clemens 2016) 5 D ++
- Documentation of the implant (manufacturer, size, filling, surface, batch number) 5 D ++
Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Treatment -

- Implant removal and complete capsulectomy including tumor removal
  
  - Oxford / AGO LOE / GR: 3a C ++

- Removal of suspicious lymph nodes, no routine sentinel-node biopsy, no axillary dissection

  - Oxford / AGO LOE / GR: 4 D ++

- Polychemotherapy (e.g., CHOP) when extracapsular tumor infiltration

  - Oxford / AGO LOE / GR: 4 D +

- Radiation for unresectable tumors or R1

  - Oxford / AGO LOE / GR: 5 D +/-

- Reconstruction after 1 year disease-free interval

  - Oxford / AGO LOE / GR: 5 D +
Breast Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) - Summary of the management (acc. to Noah 2017)

Periprosthetic seroma or tumor mass > 1 year after implant placement

- Exclude trauma or infection
- Ultrasound / sonography

Seroma: aspiration and cytology (when suspicious: CD30-IHC)

- Suspicious
- +ALCL

Operative exploration with biopsy of the capsule

Tumor mass

- Tumor board discussion

Confirmed ALCL cases

- Complete operative capsulectomy, tumor excision according to oncological standards
- Lymph node removal in case of suspicion, no new implants, possibly also contralaterally

Complete Resection R0

R1 or positive lymph nodes

- Clinical follow-up. Ultrasound and CT every 6 months for 2 years, then annually for 5 years
- Chemotherapy; CHOP, possibly Immunotherapy

Radiatiotherapy

+/-
Breast Cancer: Specific Situations (2/38)

Further information:

Update January 2017 – Schütz / Sinn
Update January 2016 – Thomssen / Harbeck
Update January 2015 – Solomayer / Harbeck
Update January 2014 – Fehm/Schneeweiss
Update January 2013 – Fersis/Friedrich
Update January 2012 – Lux/Lück
Update Februar 2011 – Janni/Huober
Update Januar 2010 – Mundhenke/Rody

Screened data bases:
Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

Screened guidelines:

This chapter of rare diseases cannot deliver references for every statements separately but is providing them where possible.

No references
Breast cancer: Specific situations (3/38)

No further information

References:

Breast Cancer in Young Women ≤ 35 years (4/38)

Further information:

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

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

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

References:


**Prognosis in young women**


3. Gonzalez-Angulo AM et al., Women age < or = 35 years with primary breast carcinoma: Disease features at presentation. Cancer 2005;103: 2466-2472


Chemotherapy in young women

1. Aebi S. Special issues related to the adjuvant therapy in very young women. Breast 2005, 14: 594-599 (Review)

Endocrine therapy in young women

2. C. Davies et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381,805–816
4. Love RR, Laudico AV, Van Dinh N, Allred DC, Uy GB, Quang le H, Salvador JD, Siguan SS, Mirasol-Lumague MR, Tung ND, Benjaafar N, Navarro NS Jr, Quy TT, De La Peña AS, Dofitas RB, Bisquera OC Jr, Linh ND, To TV, Young GS, Hade EM, Jarjoura D. Timing of adjuvant surgical oophorectomy in the menstrual cycle and

Benefit from trastuzumab


Benefit from temporary amenorrhoea after adjuvant chemotherapy (chemotherapy induced or GnRHa-related)


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


Genetic and fertility counselling

Breast Cancer During Pregnancy or Breast Feeding – Diagnosis and Surgery (5/38)

Further information:

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

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

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

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

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

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

The delivery should not be planned for the immediate three weeks following a chemotherapy cycle, since maternal side effects (e.g. fatigue, hematotoxicity) may increase the maternal risk for delivery-associated complications. Moreover, the placental excretion function disappears after delivery and the newborn may not be able to metabolize potential chemotherapy remainders.

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

There is neither evidence of direct damage to the fetus due to breast cancer nor of metastases into the fetus. Yet, rare placental metastases have been described.

Termination of pregnancy does not improve the prognosis of the breast cancer and thus is not considered a therapeutic option. Yet, depending on gestational age, termination may be considered if therapy options for the mother are severely compromised by the pregnancy.

Diagnosis of a malignancy during pregnancy causes extreme burden and conflicts for the pregnant women and their families touching on emotional, religious, social and ethical aspects next to medical issues. Most pregnant cancer patients want to “live long enough to see their child grow up”. Thus, decisions about continuing the pregnancy and about treatment should not only consider medical arguments but also take psychological as well as emotional needs of the pregnant patient into account.

References:

Outcome information (e.g. GBG registry):


Statement: Breast imaging & biopsy like in non-pregnant


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

Statement: Surgery like in non-pregnant patients


Statement: „Sentinel node biopsy“ during pregnancy


Reviews

1. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
Breast Cancer During Pregnancy – Neo(adjuvant) Therapy (6/38)

No further information

References:

In general


Statement: Radiotherapy during pregnancy


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


Statement: Anthracyclines: AC, EC

7. Omission of 5FU based on the same evidence as in non-pregnant patients (GIM2 study) - see also chapter on adjuvant chemotherapy: Cognetti F, Bruzzi P, De Placido S, et al. Epirubicin and cyclophosphamide (EC) followed by paclitaxel (T) versus fluorouracil, epirubicin and cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the gruppo Italiano mammella (GIM)-2 randomized phase III study. SABCS 2013: S5-06

Statement: Taxanes


Statement: MTX (e.g. CMF)

Statement: Endocrine treatment

Statement Trastuzumab during pregnancy

Statement Bisphosphonate during pregnancy


General information: Chemotherapy during pregnancy

Breast cancer During Pregnancy – Delivery and Breast-Feeding (7/38)

Further information:

These statements are derived from common sense and literature cannot fully be assigned.

References:

In general


Statements: Delivery should be postponed until sufficient fetal maturation since termination of pregnancy does not improve maternal outcome

Statements: Delivery mode like in non-pregnant; Avoid delivery ≤ 3 weeks from prior chemotherapy


Statements: If further systemic therapy is needed after delivery, breast feeding may be contraindicated depending on drug toxicities

1. Williams Obstetrics lecture book
No further information

No references
Pregnancy Associated Breast Cancer: Outcome (9/38)

Further information:

The outcome of pregnant breast cancer patients do not seem to be inferior to those being non pregnant. Data investigating this topic are inconsistent incorporating pregnant patients and PABC. A recent study however demonstrated a poorer survival for PABC. Most investigations did not report on the applied therapy which might be a confounding factor.

Pregnancy after breast cancer is safe and does not compromise the outcome. A healthy mother effect might be the reason, however, larger case series including also patients with advanced disease proposed additional effects.

References:

In general


Statement: Breast cancer during pregnancy / lactation: Outcome not compromised, if treated adaequately


Statement: Pregnancy and lactation after breast cancer: Outcome not compromised

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

Review articles

Geriatric Assessment (10/38)

Further information:

There is no accepted definition of the “older patient” but criteria exist for the assessment of biological age. The distinction between fit patients, vulnerable patients and frail patients has been established. Geriatric evaluation is an optimal tool for individually assessing the feasibility of treatment.

References:

Treatment for Fit Elderly Patients (11/38)

Further information:

Chemotherapy is feasible in fit elderly pts. The first randomized prospective trial in >600 pts. Demonstrated a survival benefit for patients treated with AC or CMF compared to those treated with Capecitabine alone. In an unplanned subset analysis, patients with hormone receptor negative disease derived the highest benefit from the combination therapy. Another German trial (ICE II) is investigating a combination of capecitabine with nab-paclitaxel compared to EC/CMF. In a retrospective analysis of four german randomized (neo)adjuvant trials taxanes seem feasible. Sequence therapies should be preferred; paclitaxel weekly seems to be the preferred taxane regimen in terms of toxicity for elderly pts. The study by Jones et al. evaluating TC as anthracycline free regimen showed especially good results in pts. older than 65 years.

In respect to older patients, current data increasingly suggest that the operation of the axilla could be avoided in cases of small tumours and a clinically negative axilla. Martelli et al. presented the update of a study including 671 patients ≥ 70 years (172 with axillary dissection and 499 patients without an operation of the axilla) at a median follow up time interval of 15 years. There was no significant difference in mortality within this group in the case of pT1 cN0 disease (10.7% versus 10.7%, p=0.836).

References:


Statement: Treatment according to standard


Statement: Surgery similar to „younger“ age


**Statement: Endocrine treatment (endocrine resp.)**


**Statement: Chemotherapy in pts. < 70 years**


Statement: Chemotherapy in pts. > 70 years:


Statement: Radiotherapy

Recently the long term results of a randomized phase 3 trial investigating the role of radiotherapy in elderly patients with breast conserving was reported. Patients 70 years or older with a clinically negative axilla, T1 tumors, breast conserving surgery, and hormone receptor positive tumor were randomized to Tamoxifen and radiation or to tamoxifen alone. Half of the pts were older than 75 years and around 60 % had no axillary surgery. Distant disease free survival and overall survival at 10 years were without significant difference between the groups. Local relapse was rare however higher in the no radiation arm (Breast: 2% vs 9%; Axilla: 0 % vs 3%). In a selected low risk population (T1, N0,) in elderly patients (< 70 years) with ER positive disease radiotherapy may be omitted when endocrine treatment with tamoxifen is planned.

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


**Statement: Trastuzumab**


Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (12/38)

Further information:

Frailty is a factor that is crucial in modern times for assessing older patients who are fit to undergo more invasive/aggressive management. The presence of multiple co-morbidities also affects outcome of surgery and/or adjuvant treatment for older breast cancer patients and can increase the risk of death from causes other than breast cancer. There thus may circumstances where non-operative therapies or even no treatment may be considered preferable due to these patients’ factors and evaluations.

References:

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

Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):


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


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


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

Statement: Hypofractionated radiotherapy

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


Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (13/38)

Further information:

General:
The median age of male breast cancer is around 10 years later than in female. Survival seems to be not inferior to that of women with breast cancer. Male breast cancer patients developed secondary malignancies in more than 20% of the patients. In general the level of evidence is low and most recommendations are linked to those of postmenopausal women.

Diagnostic:
In men 80-90% of maligne breast tumors are not detected by mammography or they are covered by a gynecomastia. Ultrasound seems more effective.

Surgery:
Wide excision in male breast cancer will almost always include resection of the nipple due to the small amount of breast tissue, and there is some evidence that this is not the most effective method of local control. To establish axillary status in clinically node-negative cases evidence is building up of the accuracy and low morbidity associated with sentinel-node biopsy in women. The technique has also been used in men with similarly encouraging results and sentinel node biopsy will probably become standard practice in the future for node-negative male breast cancer.

Genetic counselling:
Approximately 3-5% of female breast cancers are thought to result from autosomal dominant inheritance, particularly \textit{BRCA1} and \textit{BRCA2} mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in \textit{BRCA2} than \textit{BRCA1} families. In a southern Californian population, there were no \textit{BRCA1} mutations in 54 patients with male breast cancer, whereas there was a \textit{BRCA2} mutation in two (4%) patients. In 94 patients in the UK there were no germline \textit{BRCA1} mutations, but five (6%) patients had \textit{BRCA2} mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations with in the \textit{BRCA2} gene and risk of breast cancer.

Radiotherapy: Adjuvant radiotherapy has been delivered proportionally more frequently to men with breast cancer than to women, because the disease was more advanced locally in men and thought to be more aggressive. There is no evidence, however, that stage by stage the indications for radiotherapy should be different in men than in women. However,
retrospective studies that investigated the effects of radiotherapy in male breast cancer have not clearly shown a survival benefit.

References:

International registry:


General:


Statement: Diagnostic work up as in women
Statement: Mammography


Statement: Ultrasound


Statement: Standard-surgery: Mastectomy - men


Statement: Sentinel-node excision (SNE)


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


Statement: Genetic counselling if 1 additional relative affected (breast/ovarian cancer)

1. Ottini L et al. BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Res Treat. 2008 Sep 26
Statement: Screening for 2nd malignancies according guidelines


Statement: Systemic therapy


Review articles

Male Breast Cancer: Systemic Therapy (14/38)

Further information:

Adjuvant chemotherapy: LoE: 4; References 1-4 (retrospective analysis, case series)
Adjuvant CMF chemotherapy was associated with an improvement in disease-free and overall survival. Only 50% of the patients (N=24) actually received the planned 12 cycles of CMF due to side effects.

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)
Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free 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**

Benefit from Trimodal Treatment in Inflammatory Cancer (15/38)

Further information and references:

Survival benefit by trimodal treatment (NACT, MRM, RT) (LoE 2b B AGO++)

**Inflammatory Breast Cancer (IBC; cT4d) (16/38)**

*Further information:*

There is little information on inflammatory breast cancer (IBC) alone. Most retrospective analysis focus on T4 carcinomas without separating T4d cancer. Primary IBC is probably a distinct biological entity compared to non IBC. Prospective randomised studies for the diagnosis and treatment of patients suffering from inflammatory breast cancer are still missing. The matter of current updates is aiming on the definition, including the confirmation of an invasive carcinoma as well as clinical signs of the skin affection \( \geq 1/3 \) 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:*

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

Survival benefit by trimodal treatment (NACT, MRM, RT) (LoE 2b B AGO++)


**Statement: Staging**


**Statement: Preoperative chemotherapy**


**Statement: Regimens as in non-inflammatory BC**


Statement: in HER2 positive disease addition of trastuzumab and pertuzumab


Statement: in HER2 negative disease addition of bevazizumab


Statement: Mastectomy after chemotherapy


Statement : Sentinel lymph node


Statement: Radiotherapy


Statement: Postoperative systemic therapy as in non-inflammatory BC


Reviews

Axillary Metastasis in Occult Breast Cancer (Cancer of Unknown Primary (CUP-Ax) (17/38)

Further information:

The incidence of axillary metastasis in carcinoma of unknown primary (CUP-Ax) is < 1% of all cases with axillary nodal metastasis (Pentheroudakis, 2010). In the great majority of cases the metastasis is due to a primary breast cancer, and only rarely secondary to another malignancy (Lanitis, 2009). Pathologically, about half of the cases are positive for estrogen receptors, and one third is HER2-positive (Montagna, 2011). Outcome is similar or better, compared to breast cancer with similar biology and stage (Sohn, 2014).

References:

Guidelines:

Reviews:


Pathology


Outcome

Axillary Metastasis in Occult Breast Cancer (CUP-Ax) - Imaging Diagnostics - (18/38)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in $\leq 75\%$ of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management (Fehm 2013, Ko 2007). MRI is considered reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour (Lalonde 2005). Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial (Varadhachary 2004). All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinanalysis, fecal occult blood test (Jerusalem 2006).

References:

Statement: Mammography / Breast ultrasound / Breast MRI

Statement: Staging


Statement: PET

Axillary Metastasis in Occult Breast Cancer (CUP-Ax) - Pathology - (19/38)

Further information and references:

Immunohistochemistry

Pathology workup of axillary metastasis in carcinoma of unknown primary is directed at excluding primaries other than breast cancer and identifying the molecular phenotype of the tumour metastasis. Because of the overwhelming probability of a primary breast cancer, it is recommended use routine IHC (ER, PgR, HER2, Ki67) markers, which are commonly used for the characterization of primary breast cancer (Montagna 2011). This should be supplemented by GATA3, a marker that is positive in most breast cancers, especially hormone-receptor positive tumor type, but has been reported to be positive also in 69% of ER-negative breast cancer (Ordonez 2013). In case of a triple-negative phenotype, other markers, such as SOX10, TTF1, and others are useful (Cimino-Mathews 2013, Provenzano 2015). This may be difficult in the individual patient (Wang 2013). Only rarely, a more generic approach may be necessary to characterize the disease (Wittekind 2008, Oien 2009)


**Gene expression profiling and other molecular approaches in CUP disease**

The use of gene expression profiling for characterizing CUP disease has described using various codesets (Bender 2009, Monzon 2010, Tothill 2015, Varadachary 2008). However most studies are lacking independent verification, and may not be accurate in defining the tissue of origin (Ades 2013, Greco 2010). However, more recently epigenetic profiling has been described as an alternative method to gene expression profiling (Moran 2016), and also genomic profiling may be useful in CUP disease to characterize the tumor for possible targeted therapy (Ross 2015).


Axillary Metastasis in Occult Breast Cancer (CUP-Ax) - Treatment - (20/38)

Further information:

A systematic review of 24 retrospective studies enrolling 689 patients with axillary metastases of unknown origin showed that axillary CUP is associated with similar presentation, biology and outcome to node positive overt breast cancer and should be treated accordingly (Pentheroudakis 2010). However, the surgical treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal 2005) Probably these patients need to be treated as typical stage II patients. (Matsuoka 2003, Pavlidis 2003). The management of axillary node metastases in women with adenocarcinoma should be the same as the management of patients with lymph node metastases in breast cancer. This is emphasized by current treatment guidelines (NICE 2010, ESMO 2011, DGHO 2014). If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed (Buqat 2002). Radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unknown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C+/+-]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% (p<0,001) (Barton 2011), and a trend towards reduced ipsilateral breast tumour recurrence in patients who received radiotherapy was observed in another study (Masinghe 2011).

References:

Guidelines:


Reviews:


Statement: Axillary dissection


Statement: Mastectomy without (in-)breast tumor:
LoE: 4; References 1-4 (retrospective analysis, case reports)


Statement: Breast irradiation if breast MRI is negative


Statement: Systemic treatment according N+ tumor


Paget’s Disease of the Breast (21/38)

Further information:

Paget’s disease of the nipple is an uncommon presentation of invasive or non-invasive carcinoma, or, more rarely, occurs without any underlying neoplasia. Clinically an eczematoid, erythematous weeping or crusted lesion with irregular borders is usually present. Nipple discharge and ulceration may occur, and an associated breast tumor may be palpable. Following the histologic confirmation of Paget’s disease, the underlying malignancy of the breast should be sought for and treated accordingly. Paget’s disease and the associated breast cancer usually is a HER2-positive disease.

References:

Clinical Presentation:

Pathology and Immunohistochemistry


Paget’s Disease of the Breast - Diagnosis (22/38)

No further information

References:

Imaging:


Pathology:

http://doi.org/10.1111/j.1365-2559.2010.03665.x
Paget’s Disease of the Breast - Therapy (23/38)

No further information

References:

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

Treatment of isolated Pagets’s disease


Statement: Sentinel-node excision (SNE)

Borderline and Malignant Phyllodes Tumor (24/38)

Further information:

Phyllodes tumors (PTs) of the breast are biphasic neoplasms composed of epithelium and a spindle-cell stroma. Currently, PTs are classified as benign, borderline, or malignant based on histopathologic features. The presence of pain (P = 0.03), tumor size > 5 cm (P = 0.005), postmenopausal status (P < 0.04), heavy cellular pleomorphism (P = 0.007), high mitotic activity (P = 0.002), tumoral grade (P = 0.006) and metastasis (P < 0.00001) were prognostic factors of poor survival. (Roa 2006, Chaney 2000). However, histologic classification does not always predict outcome. Stromal c-Kit positivity and epithelial endothelin 1 negativity are more often associated with malignant PTs; however, only positive margin status is significantly associated with tumor behavior (Esposito 2006).

References:

Review


Pathology and Outcome


Borderline and Malignant Phyllodes Tumor – Diagnosis (25/38)

No further information

References:

Imaging


Core biopsy


Borderline and Malignant Phyllodes Tumor – Surgery (26/38)

Further information and references:

Mastectomy was not found to provide a benefit in PT-specific survival compared with wide excision in malignant phyllodes tumor of the breast. Women undergoing wide excision had at the minimum similar cancer-specific mortality compared with those who received mastectomy. (Macdonald 2006, Fou 2006, Cheng 2006). Some authors have seen an improved survival after Mastectomy (Ben Hassouna 2006). An axillary lymph node dissection generally is not indicated (Mishra 2013).

Statement: Complete (wide) local excision or MRM (LoE: 2c):

The mainstay of phyllodes tumour management has traditionally consisted of surgical excision with wide tumour-free margins, generally defined by some authors as at least 10 mm (Guillot 2011). However, more recent data suggest that narrow margins are usually sufficient with phyllodes tumours (Onkendi 2014, Lin 2013, Yom 2015, Mituś 2014).

References regarding surgical margins:


Other references regarding operative management and prognosis of Phyllodes Tumors:


Statement: SNE / Axillary dissection in cN0 (LoE: 4):

Metastasis in malignant phyllodes occurs almost exclusively by hematogenous dissemination. Lymph node metastasis is very uncommon, and has been quoted as 0.6% (for malignant PT) the SEER Data base (Kim 2017), while the rate of lymph node enlargement in about 10% (Mishra 2013). Therefore, routine axillary clearance or sentinel node biopsy is not recommended (Chen 2005, Mishra 2013).


Statement: Staging (LoE 5 D, AGO+)

In malignant phyllodes tumours, the risk of developing of metastases has been described between 10% and 35%, mean 17%, as compared to 0.1% for benign and 1.6% for borderline PT (Tan 2016). Metastasis occurs mainly in lung and bone. With large series (Belkacemi 2008) distant metastasis was 3.4% for phyllloides for tumors of any grading. Therefore, patients with benign or borderline phyllodes tumours do not need extensive tumor staging, while patients with malignant phyllodes tumours a much higher rate of distant recurrences was observed. In summary, as in breast cancer, clinical staging may be worthwhile, but an additional impact of regular imaging including PET and MRI in the follow-up has not been shown.

**Statements: Systemic adjuvant therapy/ Chemotherapy (LoE: 4) and Endocrine therapy (LoE: 5)**

The treatment of local recurrent disease remains unsuccessful in most malignant phyllodes tumor patients. (Soumarova 2004). Surgery for locally recurrent tumours should aim to achieve adequate surgical margins (Tan 2006). The role of chemotherapy and hormonal manipulation in both the adjuvant and palliative settings remain to be defined (Chaney 2000, Chen 2005, Morales-Vásquez 2007, Spitaleri 2013).


Statement: Adjuvant radiotherapy, if T ≥2cm (BCT) or T ≥10cm (mastectomy)

There is conflicting evidence for the benefit of radiotherapy in phyllodes tumors, but it appears to be useful to decrease local recurrence rates in the high risk setting (Gnerlich 2014, Barth 2009, Belkacémi 2009, Mituś 2014). However, there is evidence that radiotherapy may actually improve survival for malignant phyllodes tumors (Kim 2017).


Statement: Treatment of local recurrence => R0 Resection: LoE: 4; References (retrospective analysis, case reports)


Statement: Radiotherapy, chemotherapy after R1 resection

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

Borderline and Malignant Phyllodes Tumor – Adjuvant Therapy (27/38)

No further information

No references
Sarcomas of the Breast (28/38)

*No further information*

*No references*
Primary Angiosarcoma of the Breast (29/38)

Further information:

Angiosarcoma of the breast is the most common form of non-epithelial breast malignancy. Primary angiosarcoma (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Both forms of angiosarcoma do not only differ regarding their mode of presentation, but also regarding molecular pathology, being often associated with MYC and FLT4 gene amplification. While the pathogenesis of primary angiosarcoma is unknown, the pathogenesis of secondary angiosarcoma is believed to be related to irreversible DNA damage induced by radiation, resulting in genome instability and by direct tumor induction by radiation through mutations of relevant cancer-related genes. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent.

References:

Reviews


**Primary Angiosarcoma of the Breast – Diagnosis (30/38)**

**Further information:**

Breast AS present as a large, ill defined mass and has an average tumor diameter of 4 – 5.5 cm (**Scow: 7 cm**). The imaging features of AS are non-specific in mammography and up to 33% are undetectable. On ultrasound examination, there is a heterogenous echogenicity with hyperechoic areas without acoustic shadowing. The most useful imaging technique to determine the extent of AS is breast MRI that shows hypervascular, heterogenous masses that are hypointense on T1-weighted images and hyperintense on T2-weighted images.

The grading for angiosarcoma of the breast is performed according to Rosen (1988). However, the prognostic significance of this grading system is controversial (Nascimento 2008).

**References:**

**Imaging**

Pathology


Prognostic Factors

Primary Angiosarcoma of the Breast – Therapy (31/38)

Further information:

The management of angiosarcomas at different sites were recently summarized in review. Radical surgery with complete RO resection is the primary treatment of choice. Because of the mostly large tumor sizes both in primary and in secondary angiosarcoma, simple mastectomy remains the treatment of choice. The frequency of lymph node metastasis is < 1%. Therefore, routine sentinel node biopsy is not indicated. Because of the high risk of local recurrence radiotherapy should be considered. In view of the risk of metastatic disease there is a rationale for adjuvant chemotherapy. However up to now there is no convincing evidence to support the use of adjuvant chemotherapy. Active agents in metastatic angiosarcoma are anthracylines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

References:

Surgery

Adjuvant Treatment (Chemotherapy, Radiotherapy)

Secondary Angiosarcoma of the Breast (32/38)

Further information:

Secondary angiosarcoma (AS) occurs following radiotherapy after breast conserving therapy or after chest wall irradiation after mastectomy. Therefore, the term radiotherapy-associated angiosarcoma may also be used. Another, much rarer occurrence of post-treatment angiosarcoma is in the upper limb following longstanding lymphoedema after mastectomy, with or without radiotherapy. This has also been called Steward-Treves syndrome and is not radiotherapy-associated and therefore not considered here. The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation.

The role of adjuvant radiotherapy and chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with antracycline-ifosfamide or 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.

References:


Secondary Angiosarcoma of the Breast – Therapy (33/38)

No further information

References:

Surgery


Adjuvant Chemotherapy


Adjuvant Radiotherapy


Adjuvant Hyperthermia


Further References:

3. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer 2001; 92: 172-180
Angiosarcoma of the Breast – Treatment of Local Recurrence and Metastases (34/38)

No further information

References:

Treatment of local recurrences


Treatment of metastatic and non-resectable tumors

Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) (35/38)

Further information:

Breast implant-associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a rare cancer that can develop around breast implants. In the US, the FDA reported in 2016 that 258 BIA-ALCL adverse events. BIA-ALCL occurs at a mean of eight years following implantation. Histologically, it can be characterized as a CD30+/ALK- T-cell lymphoma most commonly. The estimated incidence is less than 1 per 100,000 implants per year. The recommendation is that surgeons should consider including BIA-ALCL in breast implant informed consents. Presenting symptoms include spontaneous seroma or effusion after one year from implantation. Although common causes of a delayed seroma are infection or trauma, suspicious effusions should receive a fine needle aspiration sent for pathologic review. Routine screening or prophylactic implant removal for asymptomatic patients is not recommended.

References:

Reviews


Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Diagnosis 36/38

Further information:


For suspicious cases, patients should receive an ultrasound evaluation to confirm the presence and extent of an effusion, determine if there is presence of a mass, and evaluate regional lymph node basins for lymphadenopathy. Fine needle aspiration is performed of an effusion, which is sent to an experienced hematopathologist for culture, flow cytometry, and cytology. It is critical to include a clinical history and to direct the pathologist to “rule out BIA-ALCL” as well as to perform CD30 surface protein immunohistochemistry. Ultrasound is an acceptable screening tool for the two-thirds of patients presenting with an effusion or the one-third with a mass. PET/CT and MRI are reserved for confirmed cases and there does not appear to be a role for mammography. Physicians are strongly encouraged to include a lymphoma oncologist for medical management and future disease surveillance. Preoperative evaluation includes a bone marrow biopsy to distinguish from other systemic forms of ALCL, which have a more aggressive clinical course and poor prognosis. Patients should also receive a preoperative PET/CT scan to evaluate for baseline extent of disease, masses, and involved lymph nodes.

References:

Breast-Implant-Associated Anaplastic Large-Cell Lymphoma (BIA-ALCL) – Treatment (37/38)

Further information:


In confirmed cases of BIA-ALCL definitive treatment for most patients is removal of the implants and total capsulectomy, which includes complete resection of any mass associated with the capsule. Physicians should consider possible removal of contralateral breast implants with capsulectomy as several bilateral cases have been detected incidentally. The implant, capsule, and effusion should all be sent to pathology for evaluation. Suspicious lymph nodes should also be excised. At this time, there does not appear to be a role for routine sentinel lymph node biopsy or for full axillary dissection if no clinically positive nodes are present. Surgeons are strongly encouraged to include a surgical oncologist for resection of disease as well as resection of involved lymph nodes. Surgery should be performed with strict oncologic technique including use of specimen orientation sutures and placement of surgical clips within the tumor bed. Complete surgical resection may be sufficient treatment for the majority of patients. The role for further adjunctive therapy such as chemotherapy (CHOP regimen: cyclophosphamide, doxorubicin, vincristine, prednisolone), clinical trials of targeted immunotherapy (Brentuximab vedotin), and chest wall radiation therapy for unresectable tumors or positive margins is the subject of ongoing research.

References:


Breast-Implant Associated Anaplastic Large-Cell lymphoma (BIA-ALCL) – Summary of the Management (38/38)

No further information

No references