Breast Cancer: Specific Situations
Breast Cancer: Specific Situations

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

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

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

- Aggressive biological behavior  
  - Oxford / AGO LoE / GR: 2a B

- Benefit from chemotherapy  
  - Oxford / AGO LoE / GR: 1b A ++

- Benefit from endocrine therapy  
  - Oxford / AGO LoE / GR: 1b A ++

- Endocrine therapy (TAM), if possible 5-10 y  
  - Oxford / AGO LoE / GR: 1b B ++

- Benefit from HER2 targeted therapy  
  - Oxford / AGO LoE / GR: 2b B ++

- Benefit from CT induced temporary amenorrhoea  
  - Oxford / AGO LoE / GR: 2b B +/-

- GnRHa as ovarian protection 2 weeks prior to CT  
  - Oxford / AGO LoE / GR: 1b B +/-

- Surgery like ≥ 35 y (in particular BCT)  
  - Oxford / AGO LoE / GR: 2b B +

- Stage II–III benefit from PMRT  
  - Oxford / AGO LoE / GR: 2b C +

- Genetic and fertility counseling  
  - Oxford / AGO LoE / GR: 2b B ++
Breast Cancer During Pregnancy* or Breast Feeding

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

* Participation in register study recommended
Breast Cancer During Pregnancy*

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

* Participation in register study recommended
Breast Cancer During Pregnancy*

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

* Participation in register study recommended
Pregnancy Associated Breast Cancer*: Outcome

- **BC during pregnancy / lactation**
  - Adequate treatment is essential

- **Pregnancy and lactation after BC**
  - Outcome not compromised

* Participation in register study recommended
Geriatric Assessment

- No specific algorithm is available
- Ability to tolerate treatment varies greatly („functional reserve“)
- Comprehensive geriatric assessment (CGA) describes a multidisciplinary evaluation of independent predictors of morbidity and mortality for older individuals
  - Physical, mental, and psycho-social health
  - Basic activities of daily living (dressing, bathing, meal preparation, medication management, etc.)
  - Living arrangements, social network, access to support services

Assessment tools:
- Charlson Comorbidity Index (widely used; good predictor over a 10-year period)
- 12 prognostic indicators to estimate 4-year mortality risk
- Short screening tests (more qualitative evaluation)
- IADL (IADL = The Lawton Instrumental Activities of Daily Living Scale with 8 domains of function, that are measured), G8
- Geriatric Prognostic Index (GPI), 3 parameters in oncological patients (psychological distress or acute disease, >3 prescribed drugs, neuropsychological problems)
Treatment for Fit Elderly Patients

(Life Expectancy > 5 yrs. and Acceptable Comorbidities)

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

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

*Study participation recommended

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

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

- Reduced standard treatment
- Options extrapolated from trials in elderly:
  - No breast surgery
    (consider endocrine options)
  - No axillary clearing (≥ 60 y, cN0, rec.-pos)
  - No radiotherapy (≥ 65 y, pT1, pN0, rec.-pos)
  - Hypofractionated radiotherapy or
    IORT / IOERT as sole radiotherapy modality
  - No chemotherapy if >70 years and negative
    risk-benefit analysis

Oxford / AGO
LoE / GR

2b  C  ++
2b  C  +
2b  B  +
1b  B  ++
1b  B  +
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)
  - Genetic counselling without affected relatives
- Screening for 2nd malignancies according to guidelines

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

- **Adjuvant chemotherapy as in women**
  - 2a B ++

- **HER2-targeted therapy**
  - 5 D +*

- **Endocrine therapy**
  - Tamoxifen
    - 2b B ++
  - Aromatase inhibitors (adjuvant)
    - 2b B -*
  - Aromatase inhibitors (metastatic BC)
    - 4 C +/-
  - GnRHa and AI (metastatic BC)
    - 4 C +*
  - Fulvestrant (metastatic BC)
    - 4 C +/-

- **Palliative chemotherapy as in women**
  - 4 C ++

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

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

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

Oxford / AGO LOE / GR
## Benefit from Trimodal Treatment in Inflammatory Breast Cancer

### Median survival probability

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival Probability</th>
<th>10 years-OS</th>
<th>5 years-OS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimodal therapy</td>
<td>72 months</td>
<td>55.4%</td>
<td>37.3%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>26 months</td>
<td>42.9%</td>
<td>28.5%</td>
<td></td>
</tr>
</tbody>
</table>

### Overall survival-probability (OS)

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

### Multivariate analysis of OS

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

Axillary Metastasis in Carcinoma of Unknown Primary (CUP)

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

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

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

- **Histological verification**
- **Mammography, sonography**
  - MR of the breast if other imaging negative
- **Paget’s disease with underlying disease (e.g. invasive breast cancer, DCIS)**
  - Therapy according to standard of the underlying disease
  - Surgery must achieve R0
  - Wide excision (like DCIS) + radiotherapy
- **Isolated Paget’s disease of the NAC:**
  - Surgery must achieve R0
  - Surgical resection only, no adjuvant radiotherapy
  - Sentinel-node excision (SNE)
Malignant and Borderline Phyllodes Tumor

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

Treatment of Primary Disease:

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

Oxford / AGO
LOE / GR

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

*Therapy in specialized centres recommended
Sarcoma / Angiosarcoma of the Breast
Treatment of local recurrence and metastases

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

**Distant Metastases / Unresectable Tumors:**
- Treatment like soft tissue sarcomas
- Paclitaxel weekly / liposomal doxorubicin (in angiosarcoma)
- Antiangiogenic treatment (e.g. in angiosarcoma)
- Trabectidin (after anthracycline / ifosfamide failure in leiomyosarcoma)
**Breast Cancer: Specific Situations (2/20)**

*Further information:*

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

*Screened data bases:*
Cochrane data base (2012),  
Screened for: Clinical Trials, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Reviews

*Screened guidelines:*

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

*No references*
Breast cancer: Specific situations (3/20)

No further information

References:

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

Further information:

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

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

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

References:


Prognosis in young women

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

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

**Endocrine therapy in young women**

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

**Benefit from trastuzumab**


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


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


Genetic and fertility counselling

Breast Cancer During Pregnancy or Breast Feeding (5/20)

Further information:

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

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

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

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

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

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

There is neither evidence of direct damage to the fetus due to breast cancer nor of metastases into the fetus. Yet, rare placental metastases have been described. Termination of pregnancy does not improve the prognosis of the breast cancer and thus is not considered a therapeutic option. Yet, depending on gestational age, termination may be considered if therapy options for the mother are severely compromised by the pregnancy. Diagnosis of a malignancy during pregnancy causes extreme burden and conflicts for the pregnant women and their families touching on emotional, religious, social and ethical aspects next to medical issues. Most pregnant cancer patients want to “live long enough to see their child grow up”. Thus, decisions about continuing the pregnancy and about treatment should not only consider medical arguments but also take psychological as well as emotional needs of the pregnant patient into account.

References:

**Outcome information (e.g. GBG registry):**


**Statement: Breast imaging & biopsy like in non-pregnant**


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

Statement: Surgery like in non-pregnant patients


Statement: „Sentinel node biopsy“ during pregnancy


Reviews
1. Sophie E. McGrath Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists
Breast Cancer During Pregnancy (6/20)

No further information

References:

In general


Statement: Radiotherapy during pregnancy


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


Statement: Anthracyclines: AC, EC

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

Statement: Taxanes


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


**Statement: Endocrine treatment**


**Statement Trastuzumab during pregnancy**


Statement Bisphosphonate during pregnancy


General information: Chemotherapy during pregnancy

Breast cancer during pregnancy (7/20)

Further information:

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

References:

In general


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


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

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

1. Williams Obstetrics lecture book
Pregnancy Associated Breast Cancer: Outcome (8/20)

Further information:

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

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

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

Review articles

Geriatric Assessment (9/20)

Further information:

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

References:

Further information:

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

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

References:


Statement: Treatment according to standard


Statement: Surgery similar to „younger“ age


Statement: Endocrine treatment (endocrine resp.)


Statement: Chemotherapy in pts. < 70 years


Statement: Chemotherapy in pts. > 70 years:

Statement: Radiotherapy

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

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


Statement: Trastuzumab


Treatment for Frail Patients (Life Expectancy < 5 Years, Substantial Comorbidities (11/20)

Further information:

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

References:

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

Statement: Reduced standard treatment:

Statement: No breast surgery (consider endocrine options):

Statement: No axillary clearing (≥ 60 y, cN0, Rec pos)


Statement: No radiotherapy (≥ 70 y, pT1, pN0, Rec pos)

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

Statement: Hypofractionated radiotherapy

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

Male Breast Cancer: Diagnostic Work-up and Loco-regional Therapy (12/20)

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 BRCA1 and BRCA2 mutations. The equivalent figure for men is estimated to be between 4% and 40%. Cases of male breast cancer are much more common in BRCA2 than BRCA1 families. In a southern Californian population, there were no BRCA1 mutations in 54 patients with of male breast cancer, whereas there was a BRCA2 mutation in two (4%) patients. In 94 patients in the UK there were no germline BRCA1 mutations, but five (6%) patients had BRCA2 mutations with 20% reporting a first-degree relative with breast cancer. In neither study was there a correlation between the location of the mutations within the BRCA2 gene and risk of breast cancer.

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

References:

**International registry:**

**General:**

**Statement: Diagnostic work up as in women**

**Statement: Mammography**


Statement: Ultrasound


Statement: Standard-surgery: Mastectomy –men


Statement: Sentinel-node excision (SNE)


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


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

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

Statement: Screening for 2nd malignancies according guidelines

**Statement: Systemic therapy**


**Review articles**

Further information:

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

Adjuvant endocrine therapy: LoE: 4; References 1-6 (retrospective analysis, case series)
Male cancers are mostly endocrine responsive: 91% of male BC are ER positive and 96% PR positive. It is proved that adjuvant tamoxifen in men improves 5-year disease-free survival and OS. Tamoxifen is well tolerated with the most common side effects being: Loss of libido (29%), weight gain (25%), heat flushes (21%), mood changes (21%), and depression (17%). The use of aromatase inhibitors has to be regarded as an experimental therapy at present. Due to the different physiological prerequisites for estrogen production in men and women, the effect of lowering serum estrogen levels in men has not yet been scientifically validated. Comparing adjuvant therapy with tamoxifen to aromatase inhibitors for 257 male breast cancer patients the overall survival was significantly better after treatment with tamoxifen.

Palliative endocrine therapy: LoE: 4; References 1-4 (retrospective analysis, case series)
In the metastatic setting there are data on achievement of stable disease being the maximum response to AI. Case reports do exist for anastrozol, letrozol and also fulvestrant.

Because of the low evidence level for the treatment of male breast cancer we believe that new studies should not exclude male patients. International registries should be participated in.

References:

Statement: Adjuvant Chemotherapy


Statement Trastuzumab

Statement endocrine therapy


*Statement palliative chemotherapy*

Inflammatory Breast Cancer (IBC; cT4d) (14/20)

Further information:

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


Statement: in HER2 positive disease addition of trastuzumab and pertuzumab


Statement: in HER2 negative disease addition of bevacizumab


Statement: Mastectomy after chemotherapy


**Statement: Sentinel lymph node**


**Statement: Radiotherapy**


Statement: Postoperative systemic therapy as in non-inflammatory BC


Reviews

Benefit from Trimodal Treatment in Inflammatory Breast Cancer (15/20)

Further information and references:

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

Axillary Metastasis in Carcinoma of Unknown Primary (CUP) (16/20)

Further information:

Magnetic resonance imaging of the breast enables identification of an occult breast primary tumor in < or = 75% of women who present with adenocarcinoma in the axillary lymph nodes and can influence surgical management. Positron emission tomography scan also can be used in the diagnosis of CUPs, but its value is controversial. (Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85) MRI is also reliable in finding a breast cancer in women with axillary nodal metastases and unknown primary tumour. (Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8) All patients should have a standard evaluation including CT thorax / abdomen, thyroid ultrasound, ENT investigation, urinanalysis, fecal occult blood test. Jerusalem G: Ann Oncol 17 (Suppl 10) 2006:168-176) The appropriate treatment of the breast after an axillary presentation of CUP continues to be a controversial issue. Khandelwal AH: Am J Surg. 2005 Oct;190(4):609-13) Probably these patients need to be treated as typical stage II patients. (Matsuoka, K: Breast Cancer. 2003;10(4):330-4 / Pavlidis N: Eur J Cancer. 2003 Sep;39(14):1990-2005) The management of axillary node metastases in women with adenocarcinoma should be the same as the management of patients with lymph node metastases in breast cancer. If mammary MRI is negative, surgical treatment is not recommended and an axillary node excision should be performed. (Buqat R: Bull Cancer. 2002 Oct;89(10):869-75).

The radiation therapy of the ipsilateral breast could be considered if axillary metastases are detected in patients suffering from carcinoma of unkown primary (CUP) with inconspicuous MRI of the breast [AGO 3b/C/+/-]. 48 patients with negative MRI results were included into a non-randomised study, herein 73% were treated with radiation and 27% were observed. The median follow-up after 68 months showed a recurrence free survival in 84% versus 34% (p<0,001) [Barton et al., 2011].

A systematic review of 24 retrospective studies enrolling 689 patients with axillary metastases of unknown origin showed that axillary CUP is associated with similar presentation, biology and outcome to node positive overt breast cancer and should be treated accordingly.
References:


Statement: Mammography / Breast ultrasound/ Breast MRI

1. Lalonde L: Can Assoc Radiol J. 2005 Dec;56(5):301-8

Statement: Staging


Statement: PET

5. Varadhachary GR: Cancer. 2004 May 1;100(9):1776-85

Statement: Gene expression profiling

2. Gauri et al., JCO, 26:4442-8, 2008;
3. Horlings et al., JCO, 26: 4435-4441, 2008

_Statement: ER, PR, HER2_


_Statement: Axillary dissection_


_Statement: Systemic treatment according N+ tumor_

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


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

Paget’s Disease of the Breast (17/20)

Further information:

Paget’s disease is a rare disease, therefore separate literature is scarce.

References:

Statement: MR of the breast if other imaging negative


Statement: Wide excision (like DCIS) + radiotherapy:


Statement: Sentinel-node excision (SNE)

Statement: Paget’s disease with underlying disease (e.g. invasive breast cancer, DCIS): therapy according to standard of the underlying disease


Statement: Isolated Paget’s disease of the NAC (<5%): surgical resection only, no adjuvant radiotherapy

Review:
Further information:

Phyllodes tumors (PTs) of the breast are biphasic neoplasms composed of epithelium and a spindle-cell stroma. Currently, PTs are classified as benign, borderline, or malignant based on histopathologic features. The presence of pain (P = 0.03), tumor size > 5 cm (P = 0.005), postmenopausal status (P < 0.04), heavy cellular pleomorphism (P = 0.007), high mitotic activity (P = 0.002), tumoral grade (P = 0.006) and metastasis (P < 0.00001) were prognostic factors of poor survival. (Roa JC: Pathol Int. 2006 Jun;56(6):309 / Chaney AW: Cancer. 2000 Oct 1;89(7):1502-11).

However, histologic classification does not always predict outcome. Stromal c-Kit positivity and epithelial endothelin 1 negativity are more often associated with malignant PTs; however, only positive margin status is significantly associated with tumor behavior (Esposito NN: Arch Pathol Lab Med. 2006 Oct;130(10):1516-21).


References:

In general


Statement: Core biopsy

1. Hyun Kyung Jung, Hee Jung Moon, Min Jung Kim, Eun-Kyung Kim Benign core biopsy of probably benign breast lesions 2 cm or larger: correlation with excisional biopsy and long-term follow-up. Ultrasonography 2014;33:200-205

Statement: Diagnosis


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

References 1-4 (retrospective analysis, case reports)

1. Macdonald OK: Cancer. 2006 Nov 1;107(9):2127-33

Statement: SNE / Axillary dissection in cN0 (LoE: 4):
References 1-3 (retrospective analysis, case reports)

2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94

Statement: Staging (LoE 5 D AGO+/-)

Note: In malignant phyllodes tumours, the risk of developing of metastases has been described between 10% and 35%, mean 17%; some authors with larger series (Belkacemi et al.2008) observed only 3.4% in their series. Therefore, patients with benign phyllodes tumours do not need extensive staging diagnostics, patients with malignant phyllodes tumours having residual tumour after surgery or having a high proliferation rate (>5 mitotic counts) an higher rate of recurrences has been observed, however, most often as local recurrences. In benign phyllodes tumours, distant metastases are unknown, whilst in borderline lesions also distant metastases may occur, but less frequent than in malignant disease. In summary, as in breast cancer, clinical staging may be worthwhile, a additional impact by regular imaging including PET and MRI in the follow-up has not been shown.

2. Shingo Baba1, Takuro Isoda, Yasuhiro Maruoka, Yoshiyuki Kitamura, Masayuki Sasaki, Tsuyoshi Yoshida, and Hiroshi Honda Diagnostic and Prognostic Value of Pretreatment SUV in 18F-FDG/PET in Breast Cancer:


Statement: Systemic adjuvant therapy/Chemotherapy (LoE: 4):
References 1 (cohort studies, case reports)


Endocrine therapy (LoE: 5)


Statement: Adjuvant radiotherapy: Radiotherapy after R0 (LoE: 4):
References 1-3 (retrospective analysis, cohort studies)

2. Chen WH: J Surg Oncol. 2005 Sep 1;91(3):185-94

Statement: Adjuvant radiotherapy, if $T \geq 2$ cm (BCT) or $T \geq 10$ cm (mastectomy)


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

1. Soumarova R: Arch Gynecol Obstet. 2004 May;269(4):278-81

Statement: Radiotherapy, chemotherapy after R1 resection

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

Sarcoma / Angiosarcoma of the Breast (19/20)

Further information:

The management of angiosarcomas at different sites were recently summarized in review. Radical surgery with complete RO resection is the primary treatment of choice. Because of the high risk of local recurrence radiotherapy should be considered. In view of the risk of metastatic disease there is a rationale for adjuvant chemotherapy. However up to now there is no convincing evidence to support the use of adjuvant chemotherapy. Active agents in metastatic angiosarcoma are anthracylines, taxanes and ifosfamide. In phase 2 trials antiangiogenic drugs showed promising activity.

Reference:

In general


Primary angiosarcoma (AS) predominantly occurs in premenopausal women with a mean age of 39 years and must be distinguished from secondary (radiotherapy-associated) angiosarcoma which occurs in older patients. Angiosarcoma differs from other soft tissue sarcomas of the breast in terms of its aggressive behavior with a tendency to local recurrence and distant metastasis. At time of diagnosis 37.5% of breast AS had evidence of distant metastasis. Cases of primary AS arising in pregnancy have been described and tend to be of higher histological grade and is reported to have an especially poor prognosis. However, despite the association with young age of onset and pregnancy, there is no evidence that breast AS is hormone dependent.

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

Histologic grading is important for the assessment of prognosis with the 5-year recurrence free survival of 76% for low grade AS and 15% for high grade AS but reported survival data differ widely. The role of adjuvant radiotherapy and chemotherapy is controversial. In a recent study, 29 of 69 patients received adjuvant combination chemotherapy with anthracycline-ifosfamide or gentcitabine-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. Thereforere, the role of adjuvant chemotherapy for AS of the breast remains unclear.

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

The risk of radiotherapy-associated angiosarcoma is maximal 5-10 years postradiation.

Current data show that not the type of operation in the case of sarcomas of the breast, particularly the angiosarcoma, a serious disease that could appear 10-15 years after radiation therapy, but factors such as size, grading and especially the adequate safety margins are important diagnostic factors. Thus, breast conserving surgeries could be performed with larger safety margins, if feasible and after given consent of the associated risk [AGO 4/C/++] (Al-Benna et al. 2010; Voutsadakis et al., 2011). It should be diagnosed through punch biopsy not via fine-needle biopsy. Postoperatively an anthracycline-based chemotherapy in combination with radiotherapy could be considered particularly in high-risk situations [AGO 4/C/+/-] (Barrow et al., 1999). If metastases have already occurred, paclitaxel as well as liposomal doxorubicin should be applied especially in patients with angiosarcoma. In case of unsuccessful treatment with anthracyline and ifosfamid, trabectedin could be used in patients suffering from leiomyosarcoma [AGO 2b/B/+] (Schöffski et al., 2011).
References:


Sarcoma / Angiosarcoma of the Breast Local recurrences and metastases (20/20)

No further information

References:

Hyperthermia: