Loco-regional Recurrence
Loco-regional Recurrence

- **Version 2002:** Brunnert / Simon

- **Versions 2003–2015:**
  Audretsch / Bauerfeind / Costa / Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Hanf / Harbeck / Lisboa / Maass / Mundhenke / Rezai / Solomayer / Souchon / Thomssen

- **Version 2016:** Rezai / Budach / Wenz
## Loco-regional Recurrence

### Incidence and Prognosis

<table>
<thead>
<tr>
<th>Localization</th>
<th>Frequency (%)</th>
<th>5-y. Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral recurrence(^1)</td>
<td>10 (2–20)</td>
<td>65 (45–79)</td>
</tr>
<tr>
<td>(post BCT + irradiation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest wall(^1)</td>
<td>4 (2–20)</td>
<td>50 (24–78)</td>
</tr>
<tr>
<td>(post mastectomy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As above plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supraclavicular fossa(^2)</td>
<td>34%</td>
<td>49% (3-y. OS)</td>
</tr>
<tr>
<td>Axilla:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ALND(^1)</td>
<td>1 (0.1–8)</td>
<td>55 (31–77)</td>
</tr>
<tr>
<td>After SNB(^4)</td>
<td>1</td>
<td>93%</td>
</tr>
<tr>
<td>Multiple localizations(^2)</td>
<td>16 (8–19)</td>
<td>21 (18–23)</td>
</tr>
</tbody>
</table>

Loco-regional Recurrence Staging

Examinations before treatment:

- Tissue Biopsy
- Reassessment of ER, PR, HER2
- Complete re-staging

<table>
<thead>
<tr>
<th>Examination</th>
<th>Oxford</th>
<th>AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Biopsy</td>
<td>5</td>
<td>D ++</td>
</tr>
<tr>
<td>Reassessment of ER, PR, HER2</td>
<td>3b</td>
<td>B ++</td>
</tr>
<tr>
<td>Complete re-staging</td>
<td>5</td>
<td>D ++</td>
</tr>
</tbody>
</table>
Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

**Increased risk for loco-regional recurrence**

- Young age
- Positive microscopic margins
- Number of involved lymph nodes
- Omitting adjuvant radiotherapy (if indicated)
- Extensive intraductal component
- Vessel invasion
- Triple negative and HER2 / HR- vs. HR+
- Grading (G3 vs. G1)
- Elevated proliferation markers: partic. Ki67;
- pT (> 2 vs. ≤ 2cm)
  - * node negative
- pN (N1 vs. N0)
- Inflammatory breast cancer
- Medial tumor localisation (vs. central/lateral)
- Obesity (Body mass index)

Oxford LoE

1a
1a
1a
1a
1b
1b
2a
1b*
2b
1b*
1a
1a
2b
4
1a
Metaanalysis: TNBC and Local Recurrence

Wang et al., Surg Oncol 2013 (Epub)

n = 15312 BC-patients, 22 studies, Hazard-ratios

<table>
<thead>
<tr>
<th></th>
<th>BCT</th>
<th>vs.</th>
<th>ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.75 (0.65-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>0.68 (0.60-0.76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>other subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>1.88 (1.58-2.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>2.12 (1.72-2.62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TNBC-subtype</th>
<th>vs.</th>
<th>HER2-subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILRR</td>
<td>0.69 (0.53-0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ILRR: ipsilateral locoregional recurrence
DM: distant metastasis
TNBC: triple negative breast cancer
BCT: breast conserving therapy
ME: mastectomy
Risk Factors for Locoregional Recurrences after ME


IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence …:

...> 15% chest wall: age <40; > 4 pos. nodes, 0-7 uninvolved nodes

...> 10% supraclavicular: > 4 pos. nodes

...> 5% axillary failure: age < 40; unknown tumor size, 0-7 uninvolved nodes
Metaanalysis: 7174 BCT and 5418 ME


After BCT:
HR-positive tumors show a lower risk for LRR than... triple negative tumors (RR 0.38) and.... HER2-expressing tumors (RR 0.34)

After ME:
HR-positive tumors show a lower risk for LRR than... HER2-expressing tumors (RR 0.69) and... triple negative tumors (RR 0.61)

Result:
HR-positive tumors exhibit the lowest rate of local recurrence.
Loco-regional Recurrence
Prognostic / Predictive factors

Parameters in local recurrence to define risk for re-recurrence
- Tumor size 2a B
- Multifocality 2a B
- Localisation 2b B

Parameters in local recurrence to define risk for distant metastasis/survival
- Early (<2-3 yrs.) vs. late recurrence 2b B
- LVSI/Grade/ERneg/positiv margin (if > 2 factors pos.) 3b B

Predictive factors for treatment considerations
- HER2 2b B ++
- ER and PgR 2b B ++

N = 6020 pat., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:
- TTR <48 months
- LVSI (of the LRR)
- ER negative LR-tumor
- high grade
- close margins of recurrent tumor

=> if ≥2 factors positive => worse OS
Ipsilateral Recurrence after BCT Surgery

- Mastectomy (aim: R0) 3b B ++
- Re-BCS with tumor-free margins 3b C +/-
- Axillary intervention after prior AxDiss if cN0 4 C -
- SNE after prior SNE if cN0 1b B +/-
- Palliative surgery in M1-situation 5 D +

(e.g. pain, ulceration, psychosocial)

*If no sentinel lymph node can identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended
Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Surgery

- **Curative situation: R0-resection**
  - Oxford AGO LoE / GR
    - 2b A ++

- **Palliative situation: Resection of deep parts of the chest wall**
  - Oxford AGO LoE / GR
    - 5 D +/-

- **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**
  - Oxford AGO LoE / GR
    - 5 D +
Loco-regional Recurrence after R0-Resection
Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- **Endocrine therapy in endocrine responsive tumors**
  
  Oxford AGO
  LoE / GR
  2b B ++

- **Chemotherapy (consider neoadjuvant)**

  2b B +

- **In case of HER2 positive disease**

  Chemotherapy + HER2 targeted therapy

  5 D +
CALOR Trial

n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection

5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy vs. 57% (44-67) without chemotherapy (hazard ratio 0.59 [95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).

Adjuvant chemotherapy was significantly more effective in ER negative disease (p_{interaction}=0.046).

Aebi et al. Lancet Oncol 2014
Locoregional Recurrence in Case R0
Resection not Likely - Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

- Endocrine therapy in endocrine responsive tumors
  - Oxford AGO LoE / GR
  - 2b B ++

- Chemotherapy (pre- or postoperatively)
  - 2b B ++

- HER2-targeted therapy in HER2-overexpressing tumors (with chemotherapy)
  - 5 D ++
Ipsilateral Recurrence after BCT Radiotherapy

After Re-BCS

- Whole breast irradiation
  (in case adjuvant radiotherapy was not performed)
- Re-breast irradiation
  (Partial breast radiation, brachytherapy, external beam RT)

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
  (14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)
Chest-Wall Recurrence after Mastectomy / Axillary Recurrence

Radiotherapy

**Chest-Wall Recurrence after Mastectomy**
- If no prior postmastectomy radiotherapy
  - Curative situation: irradiation of the chest wall +/- regional lymph nodes
  - Re-irradiation (chest wall + hyperthermia)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Wall Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no prior postmastectomy radiotherapy</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Curative situation: irradiation of the chest wall +/- regional lymph nodes</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

**Axillary recurrence**

Irradiation of axilla after R0-surgery
- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

<table>
<thead>
<tr>
<th>Situation</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irradiation of axilla after R0-surgery</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>No prior adjuvant irradiation of the axilla</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
</tbody>
</table>
### Loco-Regional Recurrence Treatment Options in Non Curative Cases

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>LoE</th>
<th>GR</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical chemotherapy (miltefosine)</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Concomitant radio-chemotherapy</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Hyperthermia (in centers listed on DKG website)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In combination with radiotherapy</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>- In combination with chemotherapy</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Intra-arterial chemotherapy</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>Electrochemotherapy</td>
<td>3b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>
**Loco-regional Recurrence (2/18)**

**Further information:**


**Guidelines:**


Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms
No references
Loco-regional Recurrence Incidence and Prognosis (3/18)

*Further information:*

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

*References:*


**Loco-regional Recurrence Staging (4/18)**

*Further information:*

The 5-year overall survival of patients with isolated loco-regional recurrence amounted to 50%. There are no data about the frequency of distant metastases detected by modern staging examinations at time of recurrence. Moreover there are no studies confirming an implication of the re-staging findings in systemic treatment or improvement of overall survival of asymptomatic patients with resectable loco-regional recurrence. Nevertheless to avoid „over- or undertreatment“ and to prevent complications the AGO recommends a re-staging in all patients with resectable recurrences.

*References:*

**Loco-regional Recurrence Risk Factors at Primary Diagnosis (5/18)**

*Further information:*

Risk factors for IBTR include tumor size, nodal status, estrogen receptor status, molecular subtype, young age, positive microscopic margins, extensive intraductal component, higher grading, vessel invasion multifocality, an extensive intraductal component, and lymphatic vessel invasion. Multivariate analysis stratified by treatment showed that age was an independent prognostic factor for local control. Systemic treatment and radiation therapy significantly reduced local recurrence.

*References:*

**Statement: Increased risk for loco-regional recurrence**


Statement: Young age


**Statement: Positive microscopic margins**


Statement: Extensive intraductal component


Statement: Vessel invasion

Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors


HER-2 positive breast cancer is associated with an increased risk of positive cavity margins after initial lumpectomy


HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Jia WJ1, Jia HX, Feng HY, Yang YP, Chen K, Su FX.

**Statement: Grading (G3 vs. G1)**


**Statement: pT (> 2 vs. ≤ 2cm)**


**Statement:** pN (N1 vs. N0)


**Statement:** pT (> 2 vs. ≤ 2cm) and Grading (G3 vs. G1) in node negative


Statement: pN (N1 vs. N0)

7. Truong PT, Jones SO, Kader HA, Wai ES, Speers CH, Alexander AS, Olivotto IA. Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative

8. Curr Oncol. 2014 Oct;21(5):e685-90. doi: 10.3747/co.21.2000 Risk factors for locoregional recurrence after postmastectomy radiotherapy in breast cancer patients with four or more positive axillary lymph nodes. Li Q1, Wu S2, Zhou J3, Sun J1, Li F1, Lin Q2, Guan X1, Lin H1, He Z1

Statement: number of involved lymph nodes


Statement: Medial tumor localisation (vs. central/lateral)

Statement: elevate proliferation marker, esp. Ki67


Statement: Inflammatory breast cancer


Statement: Nomograms


Statement: Obesity

Recent evidence for Multigene arrays predicting risk for local relapse:


Metaanalysis: TNBC and Local Recurrence (6/18)

No further information

No references
Risk Factors for Locoregional Recurrence after ME (7/18)

No further information

No references
Metaanalysis: 7174 BCT and 5418 ME (8/18)

No further information

No references
Loco-regional Recurrence Prognostic/Predictive factors (9/18)

No further information

References:

Parameters in local recurrence to define risk for re-recurrence

Statement: Tumour size

Statement: Multifocality


Statement: Localisation

Statement: Early vs. Late recurrence


LVSI/Grade/ERneg/close margins
Change from close margin to positive margin


Predictive factors for treatment considerations

Statement: HER-2

Statement: ER and PR

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence (10/18)

No further information

No references
Ipsilateral Recurrence after BCT - Surgery (11/18)

Further information:

Mastectomy is the current standard of care for ipsilateral recurrence of breast carcinoma. Some retrospective analyses showed that second conservative treatments for local relapse were feasible and gave results comparable to standard mastectomy. A repeat BCT demands tumor-free margins and an interstitial brachytherapy. However, the indication for second lumpectomy is restricted for suited patients (small-size, low-risk). As data from prospective randomized clinical trials are missing, an impaired regional tumor control (without disadvantages for overall survival) cannot be ruled out completely. In patients with distant metastases a local surgery is indicated in pain, endangered ulceration and in some cases for psychological reasons. SLNB after previous axillary surgery is technically feasible after breast conserving therapy. In case no sentinel lymph node can be identified, axillary dissection is not recommended.

References:

Statement: Mastectomy (aim: R0)

Statement: Re-BCS with tumor-free margins ± flap reconstruction


Statement: disadvantage for overall survival cannot be excluded, poor cosmetic result, impaired local tumor control


Statement: Axillary intervention (SNE/AxDiss) after prior SNE and BCS if cN0


Statement: Palliative surgery in M1-situation

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery (12/18)

Further information:

Because chest wall recurrences are not infrequently a marker of concurrent or future metastatic disease, local management with curative intent is advocated only after thorough re-staging.

References:

**Statement: Curative situation: R0-resection**


**Statement: Palliative situation: Resection of deep parts of the chest wall**


**Statement: Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**

Locoregional Recurrence after R0-Resection - Systemic Treatment (13/18)

Further information:

Systemic therapy after resected local recurrence (re-adjuvant) is associated with improved disease-free and overall survival. Endocrine treatment in hormone sensitive tumors improves disease free survival. The impact on overall survival has not been proven.

References:

Statement: Endocrine therapy in endocrine responsive disease


Statement: Chemotherapy


Statement: Trastuzumab-based therapy in HER-2 overexpressing tumors

So far, extrapolations from adjuvant HER2-directed studies and from studies in metastatic breast cancer


Cytotoxic Treatment in pts with Local Recurrent Breast Cancer (14/18)

No further information

No references
Locoregional Recurrence in case R0-resection not likely - Systemic Treatment (15/18)

No further information

References:

Statement: Endocrine therapy in endocrine responsive disease


Statement: Chemotherapy (pre- or postoperatively)


Statement: Trastuzumab based therapy in HER-2 overexpressing tumors

So far, extrapolations from adjuvant HER2-directed studies and from studies in metastatic breast cancer. It needs to be emphasized that in some of the registration studies such as CLEOPATRA locally advanced, not operable tumors had been included.
**Ipsilateral recurrence after BCT - Radiotherapy (16/18)**

*Further information:*

Repeat irradiation breast for recurrent breast cancer is feasible. If no prior radiotherapy has performed after BCS, whole breast radiation should be performed. In patients with no prior radiotherapy after mastectomy irradiation of chest wall and regional lymph nodes is recommended.

*References:*

**Statement: Whole breast radiation**


**Statement: Re-irradiation (breast)**


Statement: Curative situation: irradiation of the chest wall +/- regional lymph nodes

Chest-wall recurrence / Axillary recurrence - radiotherapy (17/18)

No further information

References:

Statement: If no prior postmastectomy radiotherapy


Statement: Re-irradiation (chest wall + hyperthermia)


Statement Axillary recurrence

Loco-Regional Recurrence - Treatment Options in Non-Curative Cases (18/18)

**Further information:**

The combination of chemotherapy and hyperthermia (HT) is a promising approach in the treatment of malignant tumors. Local hyperthermia combined with radiotherapy may be effective in the treatment of locally recurrent breast cancer, especially for previously irradiated cases, where only a reduced total irradiation dose is applicable. Care should be taken, to select experienced providers that treat accordingly to recognised guidelines. While the combination of hyperthermia and radiotherapy has been used for several decades and shown its efficacy in prospective randomized trials, the combination of chemotherapy and hyperthermia (HT) has much less intensively been studied in breast cancer. Few recent papers report on trimodal therapeutic attempts: chemotherapy, radiotherapy plus hyperthermia, the additional benefit of chemotherapy is not quite clear.

**References:**

Statement: Topical chemotherapy (miltefosine)


Statement: Concomitant radio-chemotherapy

Statement: Hyperthermia + radiotherapy +/- chemotherapy

11. Linthorst M, Baaijens M, Wijgenraad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Radiother Oncol 2015; May 19
Statement: Intraarterial chemotherapy


Statement: Photodynamic therapy


Statement: Electrochemotherapy