Loco-Regional Recurrence
Loco-regional Recurrence

- **Version 2002:** Brunnert / Simon

- **Versions 2003–2016:** Audretsch / Bauerfeind / Budach / Costa / Dall / Fehm / Fersis / Friedrich / Gerber / Göhring / Hanf / Harbeck / Lisboa / Maass / Mundhenke / Rezai / Solomayer / Souchon / Thomssen / Wenz

- **Version 2017:** Bauerfeind / Thomssen
## 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
  - Oxford LoE: 5
  - AGO LoE: D
  - Grade: ++
- Re-assessment of ER, PgR, HER2
  - Oxford LoE: 3b
  - AGO LoE: B
  - Grade: ++
- Complete re-staging
  - Oxford LoE: 5
  - AGO LoE: D
  - Grade: ++
## Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

### Increased risk for loco-regional recurrence

- **Young age**
- **Positive microscopic margins (R1) of the primary tumor**
- **Omitting adjuvant radiotherapy (if indicated)**
- **Extensive intraductal component**
- **Vessel invasion**
- **HER2 positive and triple negative > Luminal B-like > luminal A-like**
- **Number of involved lymph nodes**
- **Grading (G3)**
- **Elevated proliferation markers: e.g. Ki67;**
- **pT (> 2)**
  - * node negative
- **Inflammatory breast cancer**
- **Medial tumor localisation**
- **Obesity (Body mass index)**

### LoE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>1a</td>
</tr>
<tr>
<td>Positive microscopic margins (R1) of the primary tumor</td>
<td>1a</td>
</tr>
<tr>
<td>Omitting adjuvant radiotherapy (if indicated)</td>
<td>1a</td>
</tr>
<tr>
<td>Extensive intraductal component</td>
<td>1b</td>
</tr>
<tr>
<td>Vessel invasion</td>
<td>1b</td>
</tr>
<tr>
<td>HER2 positive and triple negative &gt; Luminal B-like &gt; luminal A-like</td>
<td>2a</td>
</tr>
<tr>
<td>Number of involved lymph nodes</td>
<td>1a</td>
</tr>
<tr>
<td>Grading (G3)</td>
<td>1b*</td>
</tr>
<tr>
<td>Elevated proliferation markers: e.g. Ki67;</td>
<td>2b</td>
</tr>
<tr>
<td>pT (&gt; 2)</td>
<td>1b*</td>
</tr>
<tr>
<td>* node negative</td>
<td>1a</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>2b</td>
</tr>
<tr>
<td>Medial tumor localisation</td>
<td>4</td>
</tr>
<tr>
<td>Obesity (Body mass index)</td>
<td>1a</td>
</tr>
</tbody>
</table>
## Metaanalysis: TNBC and Local Recurrence


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.

*most pts. were treated in the time before routine adjuvant trastuzumab use
Loco-regional Recurrence
Prognostic / Predictive factors

Parameters of the locally recurrent tumor to define the risk for re-recurrence
- Tumor size
- Multifocality
- Localisation
- Negative progesterone receptor

Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival
- Early (<2-3 yrs.) vs. late recurrence
- LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)

Predictive factors for treatment considerations
- HER2
- ER and PgR

Oxford AGO LoE / GR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Multifocality</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Localisation</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Negative progesterone receptor</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>Early (&lt;2-3 yrs.) vs. late recurrence</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>LVSI / Grade / ER-neg / positive margins</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>HER2</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>ER and PgR</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

++ indicates a higher level of evidence or recommendation.
Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

Panet-Raymond V et al., Cancer 117:2035, 2011

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)
- Re-BCS with tumor-free margins (R0)
- Axillary intervention after prior AxDiss if cN0
- SLNE after prior SLNE if cN0*
- Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial indication)

*If no sentinel lymph node can be 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
- Chemotherapy (consider preoperative)
- In case of HER2 positive disease, chemotherapy + HER2 targeted therapy

Oxford AGO LoE / GR

2b B ++
2b B +
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)
  
  - Oxford AGO LoE / GR
  - 2b B ++

- HER2-targeted therapy in HER2-positive tumors (with chemotherapy)
  
  - Oxford AGO LoE / GR
  - 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%)
- Repeated irradiation (e.g. as brachytherapy) with hyperthermia

<table>
<thead>
<tr>
<th>Oxford AGO LoE / GR</th>
<th>3b</th>
<th>C</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b C +/-</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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 (2b B +)
  - Re-irradiation (chest wall + hyperthermia) (1b B +/-)

Axillary recurrence
Irradiation of axilla after R0-surgery
- No prior adjuvant irradiation of the axilla (3b C +)
- Adjuvant irradiation of the axilla (5 D +/-)
### Loco-Regional Recurrence
Treatment Options in Non Curative Cases

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>LoE</th>
<th>GR</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<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>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>In combination with radiotherapy</td>
<td>4</td>
<td>C</td>
<td>+/-</td>
</tr>
<tr>
<td>In combination with chemotherapy</td>
<td></td>
<td></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 and references:


Guidelines:


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:


5. www.tumorregister-muenchen.de
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. Re-staging can be performed by conventional techniques, CT scans, MRI or Pet scans depending on practitioners choice.

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:

Informative for the whole list of factors:


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


Statement: Grading G3


Statement: pT > 2


Statement: pN (N1 vs. N0)


2. www.tumorregister-muenchen.de
Statement: pN (N1 vs. N0) and number of involved lymph nodes

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 patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73(2):357-64, 2009
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: Medial tumor localisation


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: ER-pos/PgR-pos vs ER-pos/PgR-neg or ER-neg/PgR-neg


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, but since randomized trials support the value of systemic therapy for all patients with invasive LR, reoperative SLNB, although feasible, may not be necessary.

References:

Statement: Mastectomy (aim: R0)

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

9. Reoperative Sentinel Lymph Node Biopsy is Feasible for Locally Recurrent Breast Cancer, But is it Worthwhile? Ugras S1, Matsen C1,2, Eaton A3, Stempel M1, Morrow M1, Cody HS 3rd4.

**Statement: Palliative surgery in M1-situation**

**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


Chemo Therapy by Loco-regional Recurrence (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**


**Statement Re-Irradiation of the chest wall with hyperthermia:**

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

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: Concomitant radio-chemotherapy


Statement: Hyperthermia + radiotherapy +/- chemotherapy

11. Linthorst M, Baaijens M, Wiggenraad 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