



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Loco-Regional Recurrence

Loco-regional Recurrence

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- **Versionen 2002–2018:**
**Audretsch / Bauerfeind / Brunnert / Budach /
Costa / Dall / Fehm / Fersis / Friedrich / Harbeck /
Gerber / Göhring / Hanf / Lisboa / Kühn/ Maass /
Mundhenke / Rezai / Simon / Solomayer / Souchon /
Thomssen / Wenz**
- **Version 2019:**
Dall / Wöckel

Loco-regional Recurrence Incidence and Prognosis

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Localization	Frequency (%)	5-y. Overall Survival (%)
Ipsilateral recurrence¹ (post BOT + irradiation)	10 (2–20)	65 (45–79)
Chest wall¹ (post mastectomy)	4 (2–20)	50 (24–78)
As above plus supraclavicular fossa²		
Axilla:	34%	49% (3-y. OS)
After ALND¹	1 (0.1–8)	55 (31–77)
After SNB⁴	1	93%
Multiple localizations²	16 (8–19)	21 (18–23)

¹ Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991;

² Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 201;

³ Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978;

⁴ Andersson Y, et al. Br J Surg 99(2):226-31,2012

Loco-regional Recurrence Staging

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Examinations before treatment

- Tissue biopsy
- Re-assessment of ER, PgR, HER2
- Complete re-staging
- „Liquid biopsy“

	Oxford		
	LoE	GR	AGO
Tissue biopsy	5	D	++
Re-assessment of ER, PgR, HER2	3b	B	++
Complete re-staging	5	D	++
„Liquid biopsy“	5	D	-

Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

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LoE

Increased risk for loco-regional recurrence

- | | |
|---|-----|
| ▪ Young age | 1a |
| ▪ Positive microscopic margins (R1) of the primary tumor | 1a |
| ▪ Omitting adjuvant radiotherapy (if indicated) | 1a |
| ▪ Extensive intraductal component | 1b |
| ▪ Vessel invasion | 1b |
| ▪ HER2 positive and triple negative > Luminal B-like > luminal A-like | 2a |
| ▪ Number of involved lymph nodes | 1a |
| ▪ Grading (G3) | 1b* |
| ▪ Elevated proliferation markers: e.g. Ki67; | 2b |
| ▪ pT (> 2) | 1b* |
| * nodal negativ | 1a |
| ▪ Inflammatory breast cancer | 2b |
| ▪ Medial tumor localisation | 4 |
| ▪ Obesity (Body mass index) | 1a |

Metaanalysis: TNBC and Local Recurrence

Wang et al, Surg Oncol. 2013 Dec;22(4):247-55.

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

BCT vs. ME

ILRR 0.75 (0.65-0.87)

DM 0.68 (0.60-0.76)

TNBC-subtype vs. other subtype

ILRR 1.88 (1.58-2.22)

DM 2.12 (1.72-2.62)

TNBC-subtype vs. HER2-subtype

ILRR 0.69 (0.53-0.91)

DM n.s.

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

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Karlsson et al. Ann Oncol 23:2852-8, 2012

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 BET and 5418 ME

Lowery AJ, et al. Breast Cancer Res Treat 133(3):831-41, 2012

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

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	Oxford		
	LoE	GR	AGO
<u>Parameters of the locally recurrent tumor to define the risk for re-recurrence</u>			
▪ Tumor size	2a	B	
▪ Multifocality	2a	B	
▪ Localisation	2b	B	
▪ Negative progesterone receptor	3b	B	
<u>Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival</u>			
▪ Early (< 2-3 yrs.) vs. late recurrence	2b	B	
▪ LVSI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
<u>Predictive factors for treatment considerations</u>			
▪ HER2	2b	B	++
▪ ER and PgR	2b	B	++

Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

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

n = 6020 pts., 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

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

Oxford		
LoE	GR	AGO
3b	B	++
3	C	+/-
4	C	-
2a	B	-
5	D	+

* 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



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- **Curative situation: R0-resection (including deeper parts of the chest wall in selected cases: HR pos, primary N-)**
- **Palliative situation: Resection of deep parts of the chest wall**
- **Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)**
- **SLNE after prior SLNE if cN0***

Oxford		
LoE	GR	AGO
2b	A	++
5	D	+/-
5	D	+
3b	B	-

Loco-regional Recurrence after R0-Resection Systemic Treatment

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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		
	LoE	GR	AGO
■ Endocrine therapy in endocrine responsive tumors	2b	B	++
■ Chemotherapy (consider preoperative)	2b	B	+
■ In case of HER2 positive disease, chemotherapy + HER2 targeted therapy	5	D	+

Chemo Therapy by Loco-regional Recurrence

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■ CALOR Trial update

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 ($p_{\text{interaction}}=0.046$).

Multivariate analysis: predictors of survival

chemotherapy for primary cancer (HR 3.55, p=0.03)

interval from primary surgery (HR 0.87, p=0.05)

Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406 | Cite as

Chemotherapie bei lokoregionärem Rezidiv

■ CALOR Trial update

Endpoint	ER-positive			ER-negative		
	CT	No-CT	HR (95%CI)	CT	No-CT	HR (95%CI)
10-yr DFS	50%	59%	1.07 (0.57 – 2.00)	70%	34%	0.29 (0.13 – 0.67)
	Interaction P-Value =0.013					
10-yr OS	76%	66%	0.70 (0.32 – 1.55)	73%	53%	0.48 (0.19 – 1.20)
	Interaction P-value =0.53					
10-yr BCFI	58%	62%	0.94 (0.47 – 0.85)	70%	34%	0.29 (0.13 – 0.67)
	Interaction P-value = 0.034					

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Locoregional Recurrence in Case of R1-Resection/Inoperability – Systemic Treatment

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

- **Endocrine therapy in endocrine responsive tumors**
- **Chemotherapy (pre- or postoperatively)**
- **HER2-targeted therapy in HER2-positive tumors (with chemotherapy)**

	Oxford		
	LoE	GR	AGO
Endocrine therapy in endocrine responsive tumors	2b	B	++
Chemotherapy (pre- or postoperatively)	2b	B	+
HER2-targeted therapy in HER2-positive tumors (with chemotherapy)	5	D	++

Ipsilateral Recurrence after BCT Radiotherapy

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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 metastasis)**
- **Radiation dose escalation (+10%)**
- **Repeated irradiation (e.g. as brachytherapy)
with hyperthermia**

	Oxford		
	LoE	GR	AGO
Whole breast irradiation (in case adjuvant radiotherapy was not performed)	3b	C	++
Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)	3b	C	+/-
Radiation of chest wall +/- regional lymph nodes (14% involved supraclavicular metastasis)	2b	B	+/-
Radiation dose escalation (+10%)	3b	C	-
Repeated irradiation (e.g. as brachytherapy) with hyperthermia	3a	C	+

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy



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Oxford		
LoE	GR	AGO

Chest-Wall Recurrence (R0-Resection) after Mastectomy

<ul style="list-style-type: none"> ■ If no prior postmastectomy radiotherapy <ul style="list-style-type: none"> ■ Curative situation: irradiation of the chest wall +/- regional lymph nodes ■ Re-irradiation (chest wall + hyperthermia) 	<p>2b</p> <p>1b</p>	<p>B</p> <p>B</p>	<p>+</p> <p>+/-</p>
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Axillary Recurrence

<ul style="list-style-type: none"> ■ Irradiation of axilla after R0-surgery <ul style="list-style-type: none"> ■ No prior adjuvant irradiation of the axilla ■ Adjuvant irradiation of the axilla 	<p>3b</p> <p>5</p>	<p>C</p> <p>D</p>	<p>+</p> <p>+/-</p>
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Treatment Options in Non Curative Cases

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- **Concomitant radio-chemotherapy**
- **Hyperthermia (in centers listed on DKG website)**
 - In combination with radiotherapy
 - In combination with chemotherapy
- **Intra-arterial chemotherapy**
- **Photodynamic therapy**
- **Electrochemotherapy**

Oxford		
LoE	GR	AGO
3b	C	+
1b	B	+
4	C	+/-
4	C	+/-
4	C	+/-
3b	C	+/-