

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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- **Versions 2002–2019:**

**Audretsch / Bauerfeind / Brunnert / Budach /
Costa / Dall / Fehm / Fersis / Friedrich / Harbeck /
Gerber / Göhring / Hanf / Kühn/ Lisboa / Maass /
Mundhenke / Rezai / Simon / Solomayer /
Souchon / Thomssen / Wenz / Wöckel**

- **Version 2020:**

Lux/Solbach

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 SLNE⁴	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“
- ¹⁸F-FDG PET-CT

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

Loco-regional Recurrence

Risk Factors at first diagnosis

Oxford LoE

Increased risk for loco-regional recurrence

Clinical factors:

- Young age
- First diagnosis with clinical symptoms
- Obesity (Body mass index)
- Non-alcoholic fatty disease of the liver
- Persistent lymphopenia after systemic therapy

1a

2b

1a

2b

4

Tumor related factors:

- Inflammatory breast cancer
- Multicentricity
- Medial tumor localisation
- Axillary lymph node metastasis and number of involved lymph nodes
- pT > 2 cm
- * node-negativ
- HER 2 +++ and tripel-negativ > Luminal B-like > Luminal A-like
- Grade G3
- Elevated proliferation markers: e.g. Ki-67
- pPR (residual disease) after NACT
- Nipple sparing mastectomy and tumor distance to nipple <1cm

2b

3b

4

1a

1a

1b*

1a

1b*

2b

2b

2b

Other factors (nomograms/risk-scores):

- Increased risk according to nomogram (f.e. INFLUENCE)
- CPS+EG Score
- Adjuvant Radiotherapy Intensification Classifier (ARTIC)

1a

2c

2b

Metaanalysis: TNBC and Local Recurrence

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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 loco-regional recurrence after mastectomy

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

IBCSG-Studie, 13 randomisierte Studien n = 8106 Patienten

Risikofaktoren für 10 J. kumulative Inzidenz ...:

→ 15% Thoraxwand	Alter < 40; ≥ 4 pos. Lymphknoten, 0-7 befallene LK
→ 10% supraclaviculär:	≥ 4 pos. LK
→ 5% axillares Rezidiv:	Alter < 40; Tumorgöße unbekannt, 0-7 nicht befallene Lymphknoten

Peng G et al. Biosci Reports 39 (9), 2019

Metaanalyse, 20 Publikation, n = 11.244 Patientinnen, pT1-2 pN0 nach Mastektomie

Risiko für Lokalrezidiv

→ Alter	HR 1,77 (p=0,001)
→ L1/V1	HR 2,23 (p<0,001)
→ Grading	HR 1,66 (p<0,001)
→ Her2-Status	HR 1,65 (p<0,027)
→ Menopausenstatus	HR 1,36 (p=0,015)
→ Resektionsränder	HR 2,56 (p=0,014)

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
- High grade
- Omitted radiotherapy at first recurrence
- Omitted chemotherapy at first recurrence

Oxford		
LoE	GR	AGO
2a	B	
2a	B	
2b	B	
3b	B	
3b	C	
3b	C	
3b	C	

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)

2b	B
3b	B

Predictive factors for treatment considerations

- HER2
- ER and PgR

2b	B	++
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 \Rightarrow 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	++
2b	B	+/-
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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	Oxford		
	LoE	GR	AGO
■ Curative situation: R0-resection (including deeper parts of the chest wall in selected cases: HR-positive, primary N-)	2b	A	++
■ Palliative situation: Resection of deep parts of the chest wall	5	D	+/-
■ Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)	5	D	+
■ SLNE after prior SLNE if cN0*	3b	B	-

* If no sentinel lymph node can be identified, axillary dissection is not recommended;
no operation outside the ipsilateral axilla is recommended

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
2b	B	++
2b	B	+
5	D	+

Chemo Therapy by Loco-regional Recurrence

■ 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

Loco-regional Recurrence Chemotherapy

■ CALOR Trial update

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

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

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Oxford		
LoE	GR	AGO

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

- | | | | |
|---|-----------|----------|-----------|
| ■ Endocrine based therapy in endocrine responsive tumors corresponding to metastatic disease | 2b | B | ++ |
| ■ Chemotherapy and targeted therapy (pre- or postoperative) corresponding to metastatic disease | 2b | B | ++ |

Ipsilateral Recurrence after BCT Radiotherapy

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After Re-BCS

- Whole breast irradiation
(in case of no prior adjuvant radiotherapy)
- Re-breast irradiation (Partial breast radiation,
brachytherapy/external beam RT, in case of prior adjuvant
radiotherapy)

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
3b	C	++
2b	B	+
2b	B	+/-
3b	C	-
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

■ 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

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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	+/-