Guidelines Breast
Version 2021.1E

Loco-Regional Recurrence

Loco-regional Recurrence

- **Versions 2002–2020:**
  Audretsch / Bauerfeind / Brunnert / Budach / Costa / Dall / Fehm / Fersis / Friedrich / Harbeck / Gerber / Göhring / Hanf / Kühn/ Lisboa / Lux / Maass / Mundhenke / Rezai / Simon / Solbach / Solomayer / Souchon / Thomssen / Wenz / Wöckel/
- **Version 2021:**
  Blohmer / Ditsch

Loco-regional Recurrence Incidence and Prognosis

Localization	10-y. incidence (%)	5-y. Overall Survival (%)
Ipsilateral recurrence[1] (post BCS + irradition)	**10 (2–20)**	**65 (45–79)**
Chest wall[1] (post mastectomy)	**4 (2–20)**	**50 (24–78)**
As above plus supraclavicular fossa[2]	**34%**	**49% (3-y. OS)**
Axilla:		
After **ALND[1]**	**1 (0.1–8)**	**55 (31–77)**
After **SLNE[4]**	1	**93%**
Multiple localizations[2]	**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, 2011;

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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	Oxford		
	LoE	GR	AGO
Examinations before treatment			
▪ Tissue biopsy	5	D	++
▪ Re-assessment of ER, PR, HER2	3b	B	++
▪ Complete re-staging	5	D	++
▪ „Liquid biopsy“	5	D	-
▪ ^{18}F-FDG PET-CT	2b	B	-

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Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE$_{Ox2001}$	GR	AGO
▪ Tumor size – pT	1a	A	++
▪ Axillary lymph node status – pN	1a	A	++
▪ Histological tumor type (mucinous, tubular etc.)	2b	B	++
▪ Grade (Elston & Ellis) – G	2a	B	++
▪ Age	2a	B	++
▪ Histologically proven peritumoral lymphatic vessel and vascular invasion (L1 V1)	1b	B	++
▪ pCR after NACT* in (luminal-B-like, HER2+, TN)	1a	A	++
▪ Increased risk of recurrence in invasive-lobular BC, cT3/4, N+	2a	B	+/-
▪ Obesity (BMI > 30 kg/m²)	1b	B	+
▪ Margins (resection status) – R0/R1	1a	A	+

* NACT = Neoadjuvant Chemotherapy

Early Breast Cancer (M0) - eBC
Prognostic Factors II

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Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ ER / PR	2a	B	++
▪ HER2 (IHC, ISH)	2b	B	++
▪ ER / PR / HER2/ Ki-67 to assess the molecular type	2b	B	++
▪ uPA / PAI-1 (Femtelle® ELISA) in N0	1a	A	+
▪ Proliferation markers			
▪ Ki-67 before, during, or after treatment	1a	B	+

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Reproducibility – Quality assurance is key for clinical decision making

- ER/PR: concordance central vs local is high (97%; Plan B, SABCS 2014)
- Grade: concordance central vs local is 68% (PlanB, JCO 2016)
- HER2: frequency of false-positive test results 6% (ASCO /CAP JCO 2013)
- Impact of routine pathologic review in N0 BC: 20% changes: grade 40%, LVI 26%, N 15%, margin 12% (JCO 2012)
- pN0 from MIRROR study: pN0 was upstaged in 22%, in central pathology review (Ann Oncol 2012)
- Ki67:
  - Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)
  - High reproducibility for low and high Ki67 levels (J Pathol 2002)
  - Standardized methodology improves analytical validity (JNCI 2020)

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-study, 13 randomised studies; n = 8106 pts

Risk factors for 10 years cumulative incidence

→ 15% chest wall	age < 40; ≥ 4 pos. lymph nodes, 0-7 pos. lymph nodes
→ 10% supraclavicular	≥ 4 pos. Lymph nodes
→ 5% local rrecurrence axilla	age < 40; tumor size unknown, 0-7 neg. lymph nodes

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

metaanalysis, 20 publications, n = 11.244 pts, pT1-2 pN0 post mastectomy

Local recurrence risk

→ age	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)
→ menopausal status	HR 1,36 (p=0,015)
→ Resection margins	HR 2,56 (p=0,014)

Early Breast Cancer (M0) - eBC
Prognostic Factors III

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Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Gene expression profiles (GEP, multigene assays, gene signatures)			
▪ MammaPrint® (N0-1)	1b	A	+*
▪ Oncotype DX® (N0-1, HR+ HER2-)	1b	A	+*
▪ EndoPredict® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Prosigna® (N0-1, HR+, HER2 -)	2b	B	+*
▪ Breast Cancer Index^{SM} (N0-1, HR+ HER2-)**	2b	B	+/-*
▪ PREDICT® algorithm (https://breast.predict.nhs.uk/)	1b	A	+
▪ Clinical-pathological score for lobular breast cancer (nodal status, tumor size, lymphovascular invasion LVI)	2b	B	+/-
▪ CTS5 Clinical Treatment Score**	2b	B	+
▪ CPS-EG Score	2b	B	+

* Should only be used in the context of clinical-pathological criteria (tumor size, nodal involvement, grade, Ki-67, ER, PR, HER2)

** estimation of late recurrence

Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	Oxford GR	Oxford AGO
▪ Disseminated tumor cells (DTC, in bone marrow)	1a	A	+/-
▪ Circulating tumor cells (CTC, in blood, Cell Search®) $	1b	A	+/-
▪ CTC before NACT (regarding OS, DDFS, LRFI)	1b	B	+/-
▪ Therapy decisions based on CTC phenotypes	3a	C	-
▪ Cell-free DNA (cfDNA, in blood, for DFS, PFS, OS)	2b[a]	B	+/-

$ Validated clinical data only available for this assay

Risk factors for another relapse

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

<u>Multivariate analysis:</u>

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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	Oxford		
	LoE	GR	AGO
▪ Mastectomy (aim: R0)	3b	B	++
▪ Re-BCS with tumor-free margins (R0) +partial breast irradiation*	2b	B	+
▪ Re-BCS with tumor-free margins (R0)	2b	B	+/-
▪ Axillary intervention after prior AxDiss if cN0	4	C	-
▪ SLNE after prior SLNE if cN0**	2a	B	-
▪ Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial indication)	5	D	+

* After tumorboard presentation

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

Mastektomy vs. BCS + partial breast irradiation

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- 1327 pts. from 7 European countries with first local recurrence 01/1995 - 06/2017

- ME vs. BCS + Brachytherapy

- Propensity Score matched control (1:1): clinical and histopathological factors

- Primary endpoint: 5-y OS; secondary endpoints: e.g. 5-J.-DFS, complications

- Median follow-up 75.4 months

- No differences in 5-J. OS and sec. Endpoints: 5-y -OS: 88 vs. 87%
  cumulative incidence 2. recurrence: 2.3 vs. 2.8%

- 5-y incidence of mastectomy after 1. recurrence 3.1%

Hannoun-Levi et al. Int J Radiat Oncol Biol Phys. 2020

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 N0)	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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	Oxford		
	LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2)			
▪ Endocrine therapy in endocrine responsive tumors	2b	B	++
▪ Chemotherapy (consider preoperative administration)	2b	B	+
▪ In case of HER2-positive disease, chemotherapy + HER2-targeted therapy	5	D	+

Loco-regional Recurrence Chemotherapy

- **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 ($p_{interaction}$=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					

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

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

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	Oxford		
	LoE	GR	AGO
According to histopathological pathohistological re-evaluation of the recurrent tumor (ER, PR, 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

	Oxford LoE	Oxford GR	AGO
After Re-BCS			
▪ Whole breast irradiation (in case of no prior adjuvant radiotherapy)	3b	C	++
▪ Re-breast irradiation (Partial breast irradiation, brachytherapy/ external beam RT, in case of prior adjuvant radiotherapy)	2b	B	+
After mastectomy			
▪ 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			
▪ 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	+/-

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Loco-Regional Recurrence
Treatment Options in Non Curative Cases

	Oxford		
	LoE	GR	AGO
▪ Concomitant radio-chemotherapy	3b	C	+
▪ Hyperthermia (in centers listed on DKG website)			
▪ In combination with radiotherapy	1b	B	+
▪ In combination with chemotherapy	4	C	+/-
▪ Intra-arterial chemotherapy	4	C	+/-
▪ Photodynamic therapy	4	C	+/-
▪ Electrochemotherapy	3b	C	+/-