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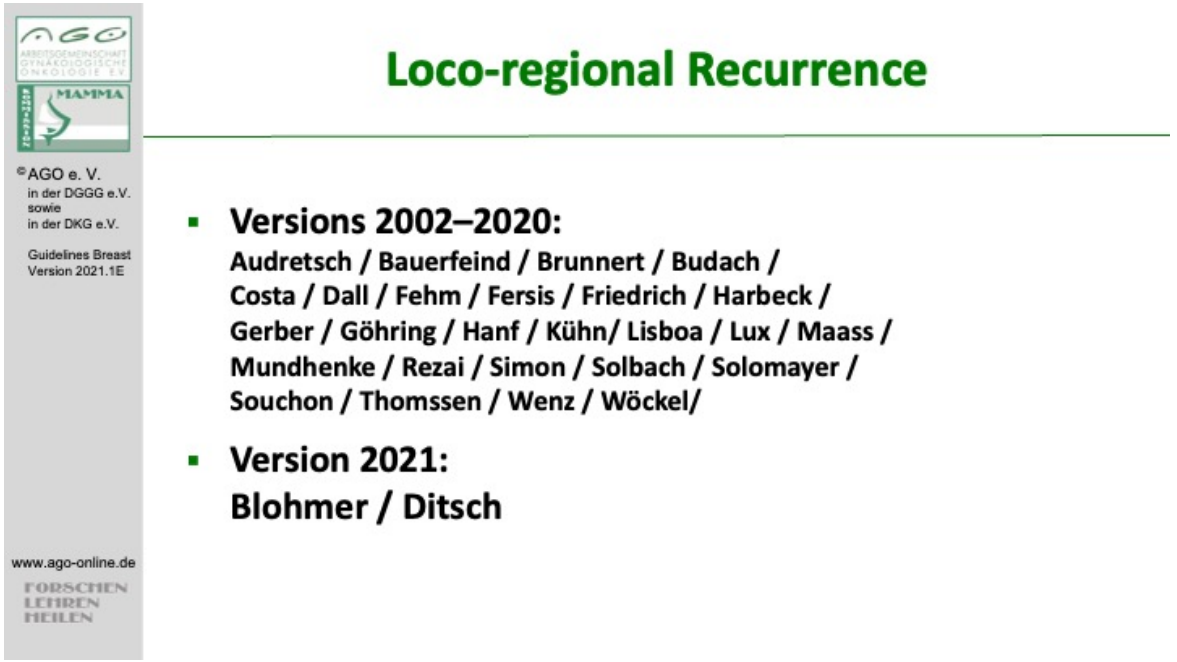
Guidelines Breast
Version 2021.1E

FORSCHEN
LEHREN
HEILEN

Loco-Regional Recurrence



Screened data bases

Pubmed 2005 - 2019, ASCO 2005 – 2019, SABCS 2009 – 2019, Cochrane data base

Guidelines

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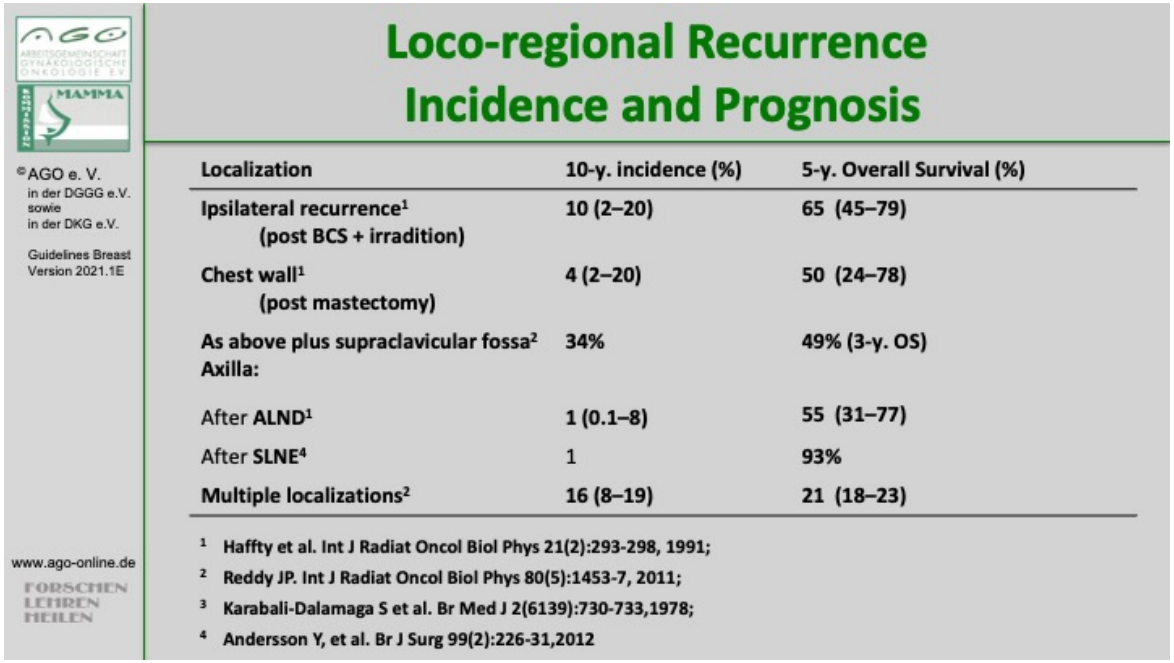

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Loco-regional Recurrence Staging

	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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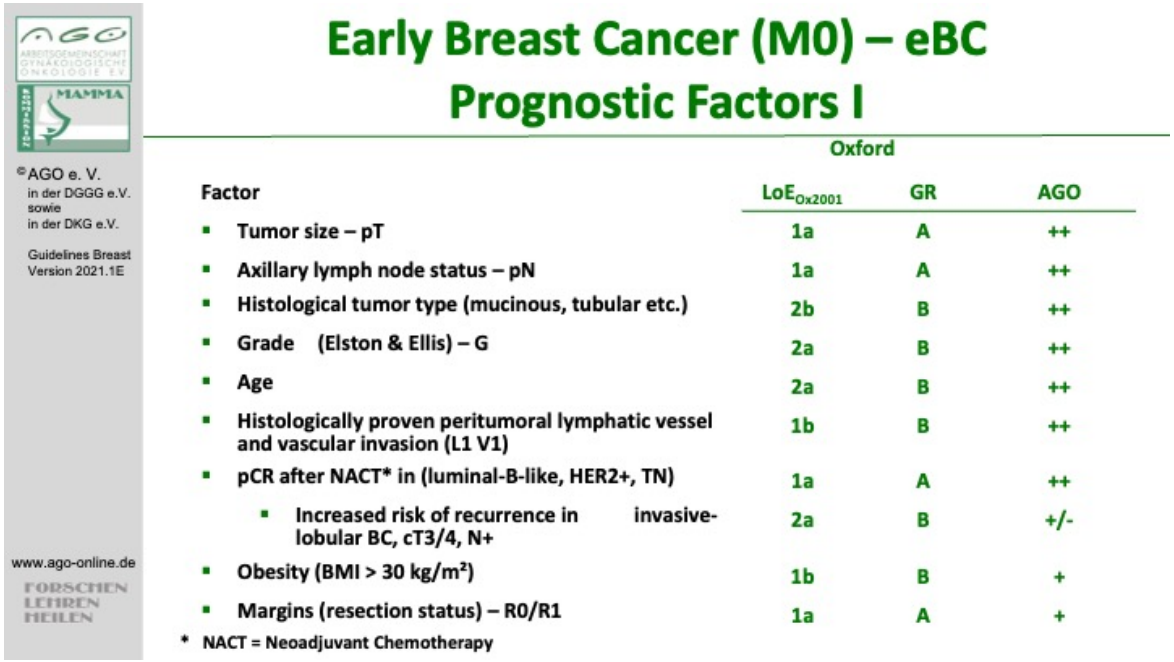

Early Breast Cancer (M0) – eBC
Prognostic Factors I

Factor	Oxford LoE_{Ox2001}	Oxford 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

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Tumor size

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Lymph node status

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Histological type (mucinous, tubular etc.)

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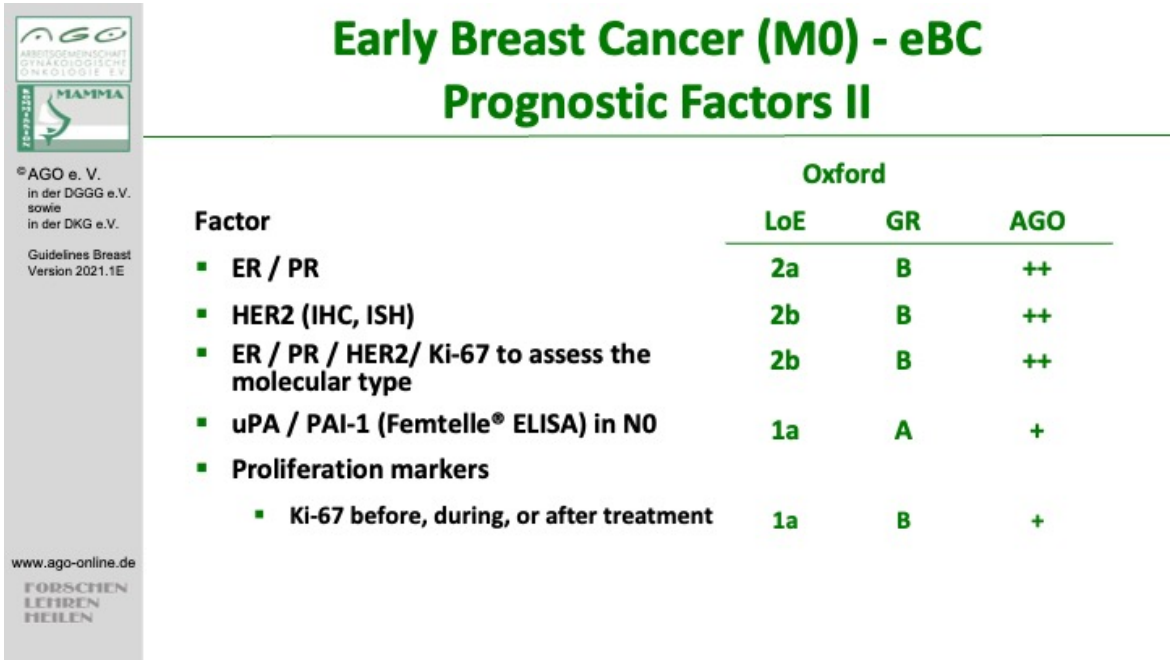

Early Breast Cancer (M0) - eBC
Prognostic Factors II

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	+

ER/PR

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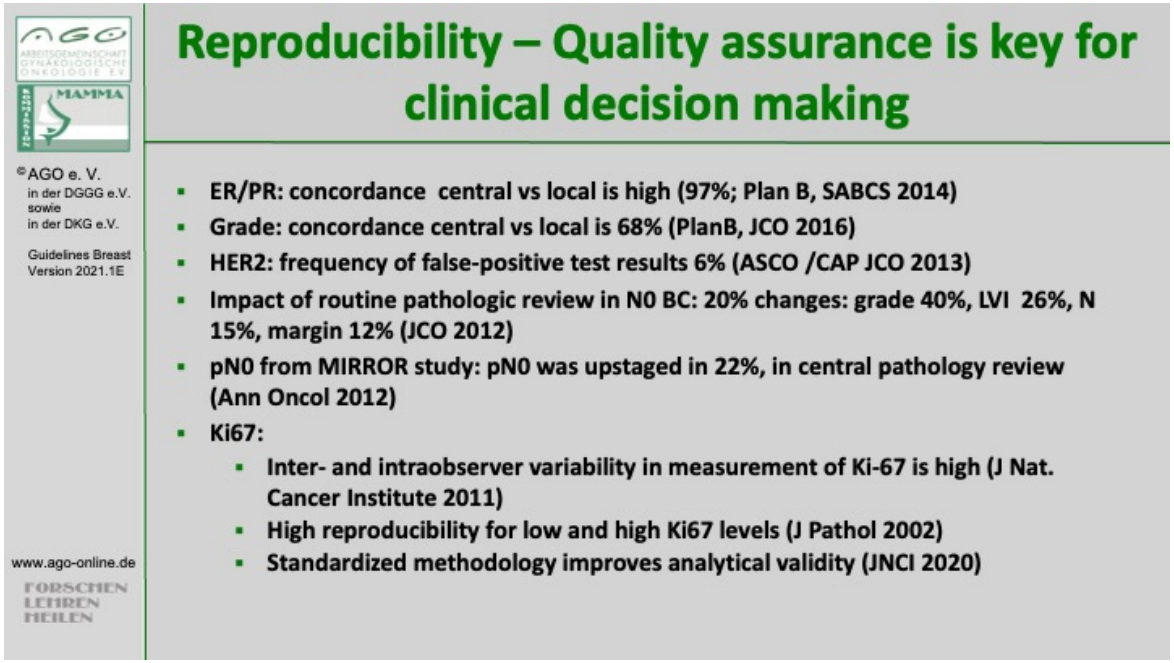

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Metaanalysis:
TNBC and Local Recurrence

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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

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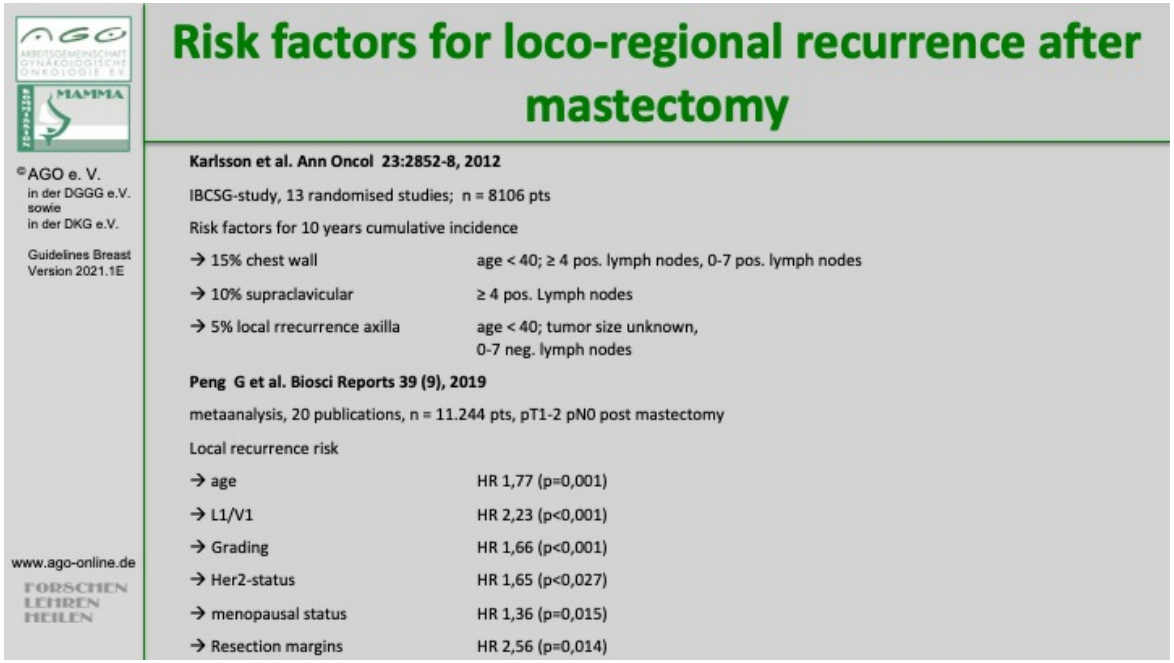

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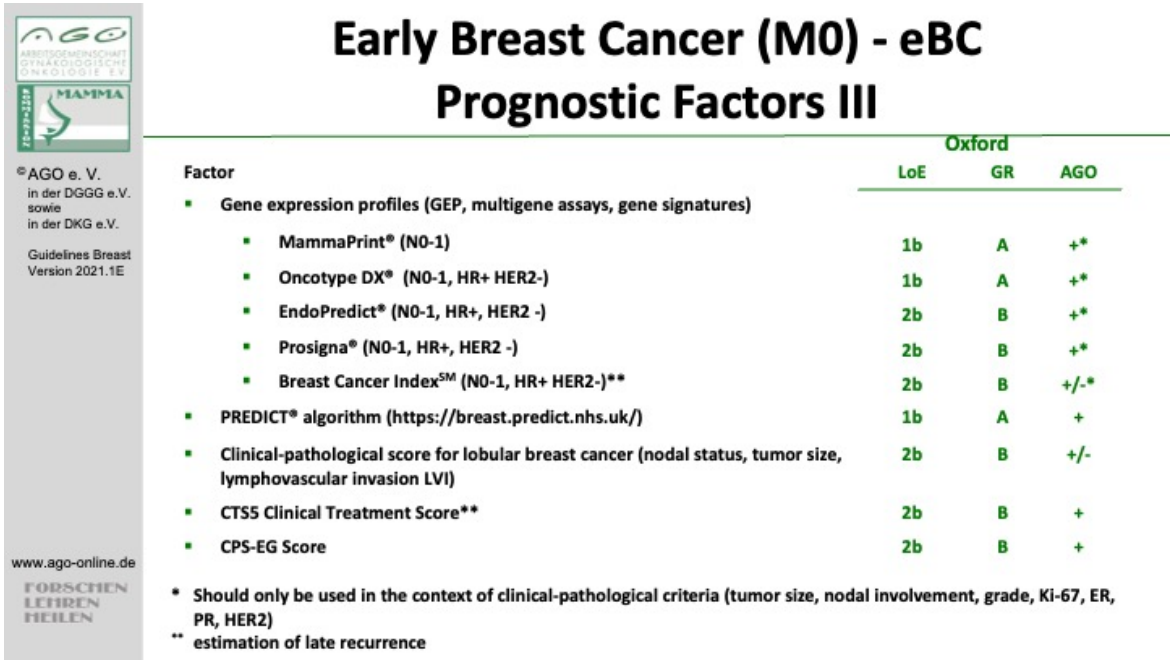

Early Breast Cancer (M0) - eBC
Prognostic Factors III

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

<u>Gene expression profiles (GEP; Multigene Assays, Gene expression signatures)</u>
(*Should only be used in the context of clinico-pathological criteria (e.g. tumor size, number involved lymph nodes, grade, Ki67) for therapeutic decision making)

<u>MammaPrint®</u>

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Lobular Score:

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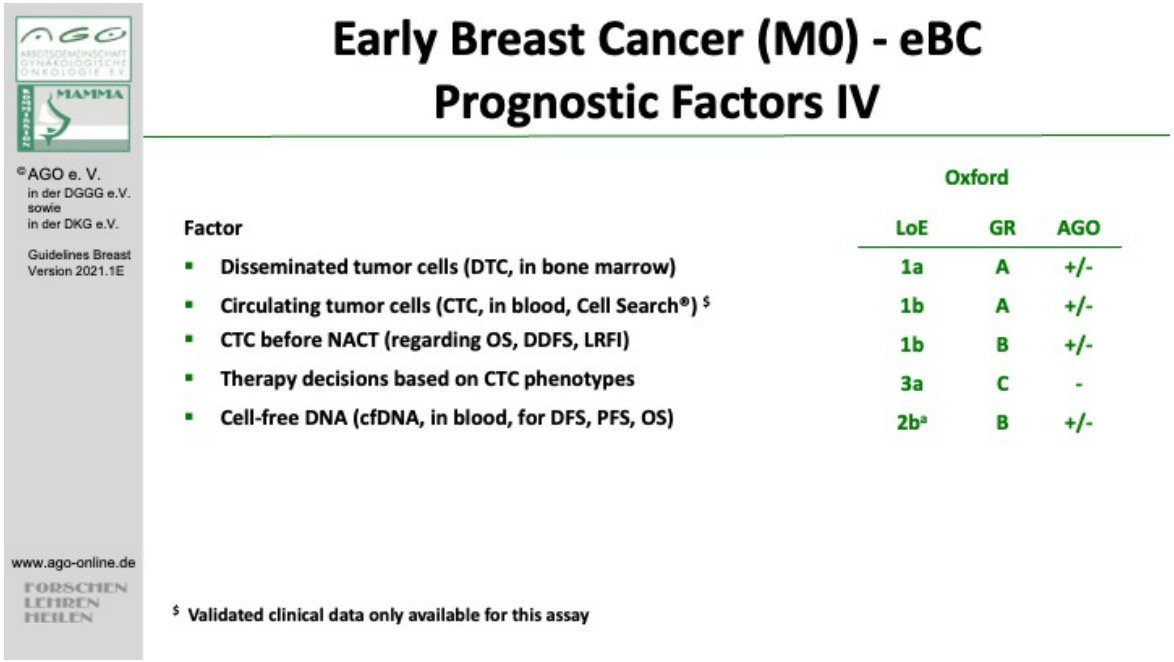

Early Breast Cancer (M0) - eBC
Prognostic Factors IV

Factor	Oxford LoE	GR	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

DTC

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CTC

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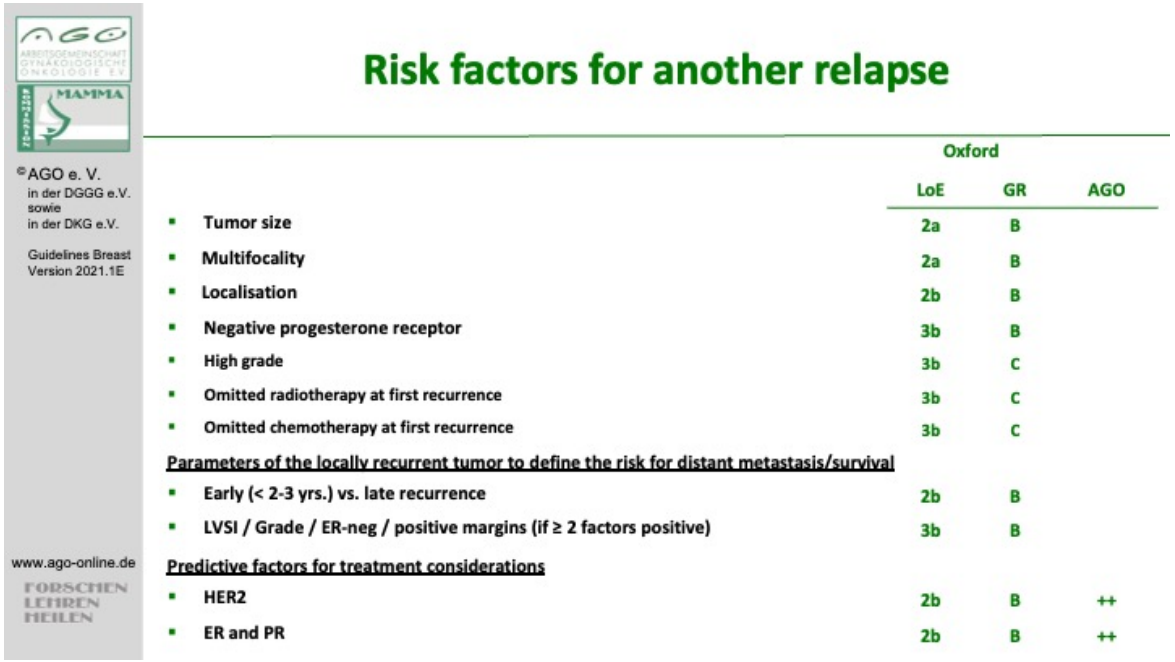

Risk factors for another relapse

	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	++

Parameters in local recurrence to define risk for re-recurrence

Statement: Tumour size

1. Wapnir IL, Anderson SJ, Mamounas EP et al; Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006
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Statement: Multifocality

1. Wapnir IL, Anderson SJ, Mamounas EP et al; Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006

Statement: Localisation

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

1. Wapnir IL, Gelber S, Anderson SJ et al; CALOR trial investigators. Poor Prognosis After Second Locoregional Recurrences in the CALOR Trial. Ann Surg Oncol. 2017 Feb;24(2):398-406

Statement: high tumour grade/ omission of chemotherapy/ omission of radiotherapy

1. Bounous VE, Novara L, Scicchitano F et al; A retrospective analysis on 197 cases of breast cancer local recurrence: Biology, treatment, and prognosis. Breast J. 2019 Nov 25. doi: 10.1111/tbj.13698

Statement: Early vs. Late recurrence

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2. Halverson KJ, Perez CA, Kuske RR et al; Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 23(2):285-91, 1992
3. Wapnir IL, Anderson SJ, Mamounas EP et al; Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 4(13):2028, 2006
4. Lee YJ, Park H, Kang CM et al. Risk stratification system for groups with a low, intermediate, and high risk of subsequent distant metastasis and death following isolated locoregional recurrence of breast cancer. Breast Cancer Res Treat. 2019 Oct 23. doi: 10.1007/s10549-019-05469-5.

LVSI/Grade/ERneg/close margins

Change from close margin to positive margin

1. Panet-Raymond V, Truong PT, Alexander C et al; Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. Cancer 117:2035, 2011

Margin width and Re-excision in breast conservativ treatment. a Danish breast coopertive group of 11.900 women.

1. A. Bodilson et al; St Antonio Breast cancer symposium Dez.2015. Increased risk of IBTR associated with final positive margin.

Predictive factors for treatment considerations

Statement: HER-2

1. Clemons M, Hamilton T, Goss P; Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001

Statement: ER and PR

1. Clemons M, Hamilton T, Goss P; Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001
2. Haffty BG, Reiss M, Beinfield M et al; Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol 14: 52–57, 1996
3. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Oncology Biol Phys 72: 1456-64, 2008

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

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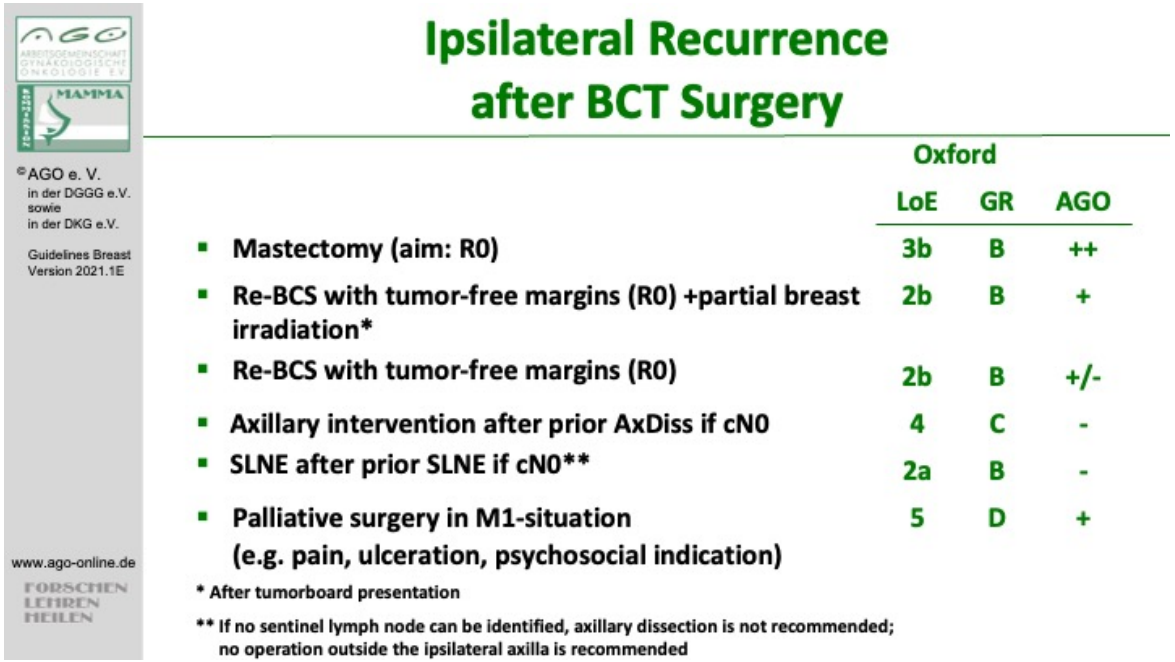
Panet-Raymond V et al. Cancer 117:2035, 2011

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



Statement: Mastectomy (aim: R0)

1. Alpert TE, Kuerer HM, Arthur DW et al; Ipsilateral breast tumor recurrence after breast conservation therapy: outcomesof salvage mastectomy vs. salvage breast-conserving surgery and prognosticfactors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
2. Shin E, Suemasu K, Sonoo H et al; Analysis of ipsilateral breast tumor recurrences after breast-conservingtreatment based on the classification of true recurrences and new primary tumors. Breast Cancer 12(2):104-11, 2005
3. Kolben T, Schwarz TM, Goess C et al; Surgical management of ipsilateral breast tumor recurrence. Int J Surg. 2015 Nov;23(Pt A):141-6.
4. NCCN (National Comprehensive Cancer Network, 2019); https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf, Version 3.2019 — September 6, 2019 (download 25. Jan. 2020)

Statement: Re-BEO with R0-Resection (+Partialbrustbestrahlung):

1. Sellam Y, Shahadi ID, Gelernter I et al; Local recurrence of breast cancer: Salvage lumpectomy as an option for local treatment. Breast J. 2019 Jul;25(4):619-624.
2. Forster T, Akbaba S, Schmitt D et al; Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation. J Contemp Brachytherapy. 2019;11(4):312-319.

3. Cozzi S, Jamal DN, Slocker A et al; Second breast-conserving therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor recurrence: a retrospective study of 40 patients. J Contemp Brachytherapy. 2019;11(2):101-107.
4. Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database.Hannoun-Levi JM, Gal J, Van Limbergen E, et al. Int J Radiat Oncol Biol Phys. 2020 Dec 29:S0360-3016(20)34722-2. doi: 10.1016/j.ijrobp.2020.12.029.

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

1. Intra M, TrifiròG, Viale G et al; Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 12(11):895- 899, 2005
2. Taback B, Nguyen P, Hansen N et al; Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. Ann Surg Oncol 13(8):1099-104, 2006
3. Port ER, Garcia-Etienne CA, Park J et al; Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. Ann Surg Oncol. 14(8):2209-14, 2007
4. Derkx F, Maaskant-Braat AJ, van der Sangen MJ et al; Staging and management of axillary lymph nodes in patients with local recurrence in the breast or chest wall after a previous negative sentinel node procedure. Eur J Surg Oncol 36(7):646-51, 2010
5. Barone JL, Feldman SM, Estabrook A et al; Reoperative sentinel lymph node biopsy in patients with locally recurrent breast cancer. Am J Surg 194(4):491-3,2007
6. Maaskant-Braat AJ, Voogd AC, Roumen RM et al; Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2013 Feb;138(1):13-20. doi: 10.1007/s10549-013-2409-1. Epub 2013 Jan 23
7. Kothari MS, Rusby JE, Agusti AA et al; Sentinel lymph node biopsy after previous axillary surgery: A review. Eur J Surg Oncol. 2012 Jan;38(1):8-15. doi: 10.1016/j.ejso.2011.10.003. Epub 2011 Oct 26.
8. Uth CC, Christensen MH, Oldenbourg MH et al; Sentinel Lymph Node Dissection in Locally Recurrent Breast Cancer. Ann Surg Oncol. 2015 Jan 7. [Epub ahead of print]
9. Ugras S, Matsen C, Eaton A et al; Reoperative sentinel lymph node biopsy is feasible for locally recurrent breast cancer, but is it worthwhile? Ann Surg Oncol. 2016 March ; 23(3): 744–748. doi:10.1245/s10434-015-5003-4.
10. Jakub JW. Sentinel Lymph Node Biopsy for Ipsilateral Breast Tumor Recurrence, Technically Feasible but Influence on Oncologic Outcomes Yet to be Completely Defined. Ann Surg Oncol. 2019;26(8):2319-2321.

11. Poodt IGM, Vugts G, Schipper RJ et al. Sentinel Node and Recurrent Breast Cancer (SNARB) study group. Prognostic impact of repeat sentinel lymph node biopsy in patients with ipsilateral breast tumour recurrence. Br J Surg. 2019;106(5):574-585.

Statement: Palliative surgery in M1-situation

1. Rapiti E. et al; Complete Excision of Primary Breast Tumor Improves Survival of Patients With Metastatic Breast Cancer at Diagnosis. Journal of Clinical Oncology 2743-2749, 2006

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

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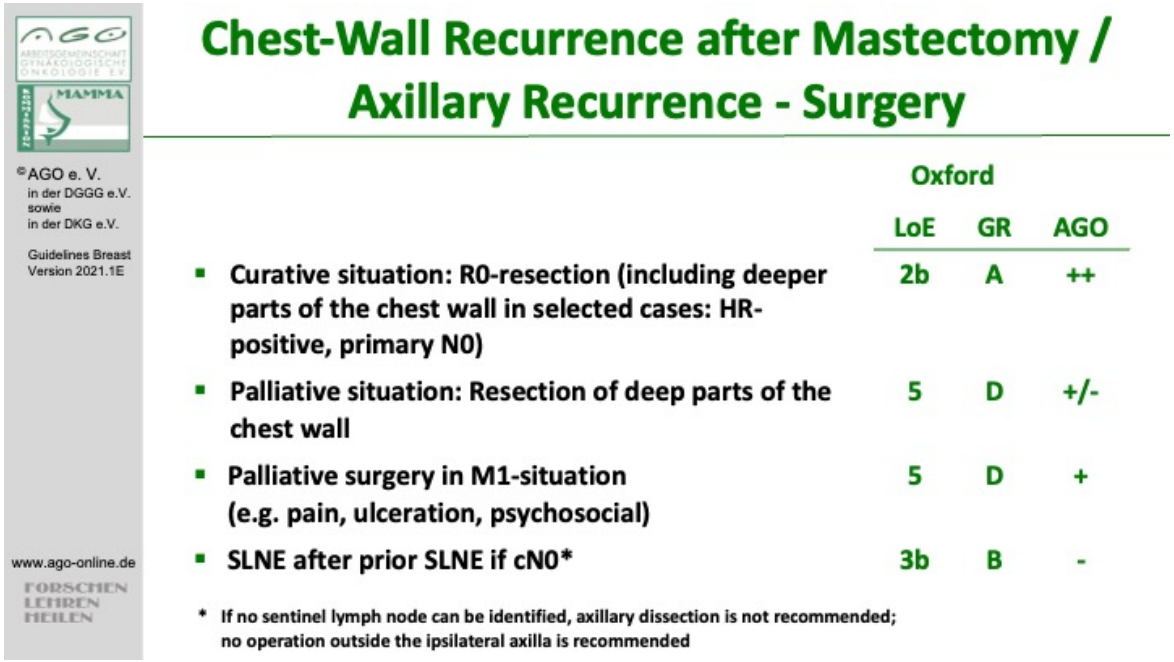


Statement: Curative situation: R0-resection

1. Mignano JE, Gage I, Piantadosi S et al; Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treatedwithout postoperative radiation therapy. Am J Clin Oncol 30(5)466-72, 2007

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

1. Mignano JE, Gage I, Piantadosi S et al; Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treatedwithout postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007
2. Pfannschmidt J, Geisbüsch P, Muley T et al; Surgical resection of secondary chest wall tumors. Thorac Cardiovasc Surg 53(4):234-9, 2005
3. Wakeam E, et al, Annals of Surgery 267: 646-55 (2018)
   Chest wall resection for recurrent breast cancer in the modern era: a systematic review and meta-analysis
4. Christopherson K, Lei X, Barcenas C et al. Outcomes of Curative-Intent Treatment for Patients With Breast Cancer Presenting With Sternal or Mediastinal Involvement. Int J Radiat Oncol Biol Phys. 2019;104(3):574-581.

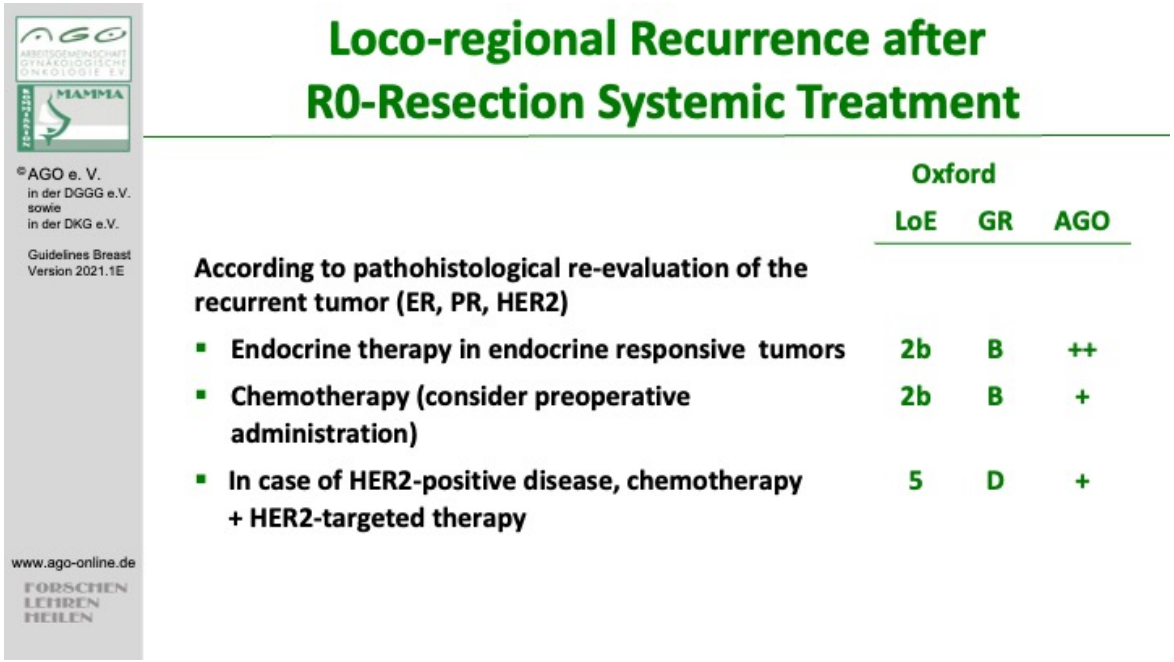
Statement: Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)

1. Rapiti E. et al; Complete Excision of Primary Breast Tumor Improves Survival of Patients With Metastatic Breast Cancer at Diagnosis.

Journal of Clinical Oncology 2743-2749, 2006

Statement: Re-SLN after SLN:

1. Ugras et al., Annals of Surgical Oncol 23: 744-8, 2016
2. Jakub JW. Sentinel Lymph Node Biopsy for Ipsilateral Breast Tumor Recurrence, Technically Feasible but Influence on Oncologic Outcomes Yet to be Completely Defined. Ann Surg Oncol. 2019;26(8):2319-2321.



Loco-regional Recurrence after R0-Resection Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2)	Oxford LoE	Oxford GR	Oxford AGO
▪ 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	+

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A et al; First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research.J Clin Oncol. 12(10):207, 1994
2. Lê MG, Arriagada R, Spielmann M et al; Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma. Cancer 94(11):2813-20, 2002
3. Halverson KJ, Perez CA, Kuske RR et al; Locoregional recurrence of breast cancer: a retrospective comparison of irradiation alone versus irradiation and systemic therapy. Am J Clin Oncol. 15(2):93-101, 1992

Statement: Chemotherapy

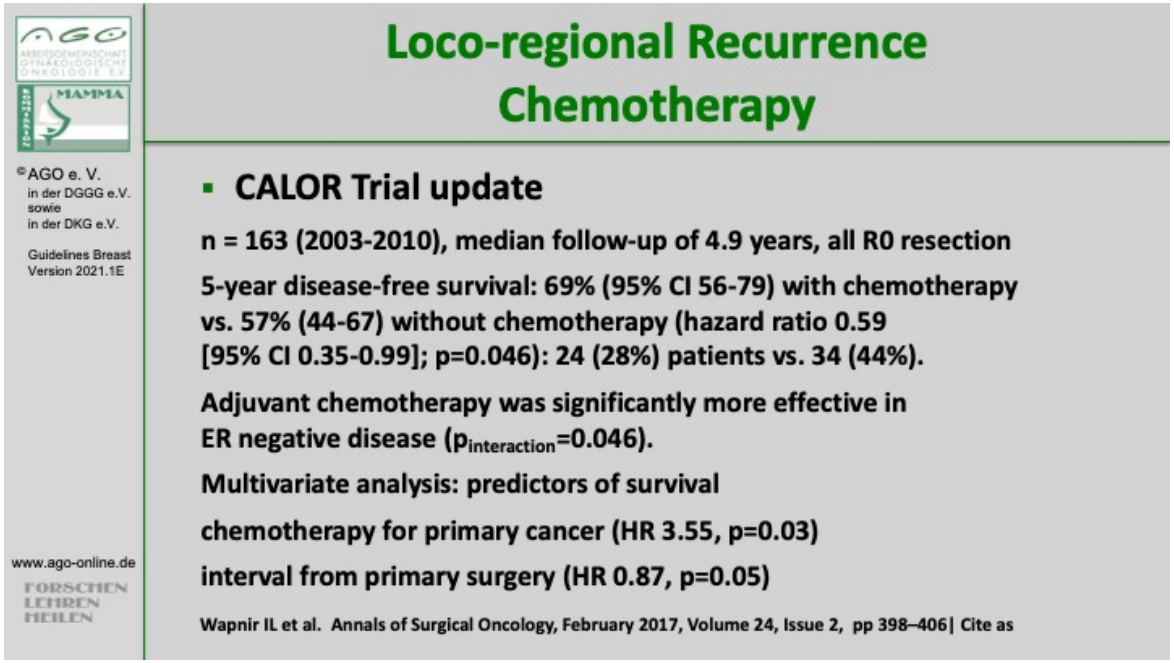
1. Easson AM, McCready DR; Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
2. Rauschecker H, Clarke M, Gatzemeier et al; Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4):CD002195. Review.
3. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008.
4. Aebi S, Gelber S, Anderson SJ et al; CALOR investigators.Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR):

a randomised trial.Lancet Oncol. 2014 Feb;15(2):156-63.
5. Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406

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

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

1. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.2 Aktualisierung August 2019, AWMF-Register-Nummer: 032 – 045OL; https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.2/LL_Mammakarzinom_Langversion_4.2.pdf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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

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- **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

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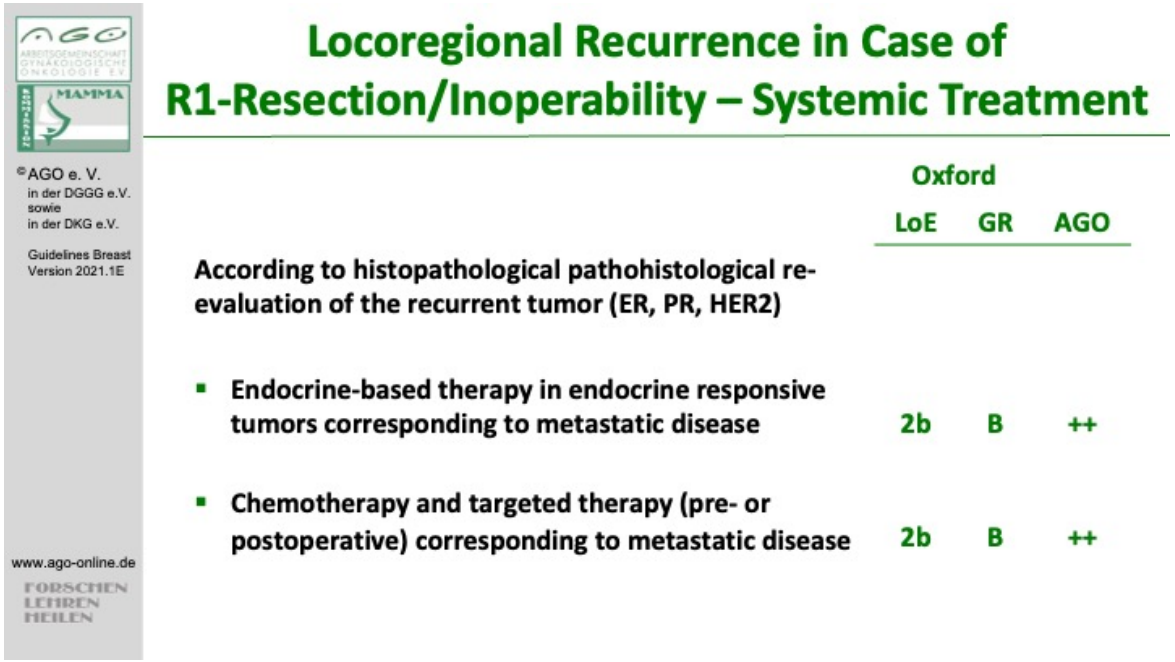


Locoregional Recurrence in Case of R1-Resection/Inoperability – Systemic Treatment

	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	++

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A et al; First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research.J Clin Oncol. 12(10):207, 1994
2. Lê MG, Arriagada R, Spielmann M et al; Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma. Cancer 94(11):2813-20, 2002
3. Halverson KJ, Perez CA, Kuske RR et al; Locoregional recurrence of breast cancer: a retrospective comparison of irradiation alone versus irradiation and systemic therapy. Am J Clin Oncol. 15(2):93-101, 1992

Statement: Chemotherapy (pre- or postoperatively)

1. Kuo SH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiat Oncol Biol Phys 72: 1456-64 (2008)
2. Tokunaga Y, Hosogi H, Nakagami M et al; A case of chest wall recurrence of breast cancer treated with paclitaxel weekly, 5'-deoxy-5-fluorouridine, arterial embolization and chest wall resection. Breast Cancer. 2003;10(4):366-70.
3. Easson AM, McCready DR; Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
4. Rauschecker H, Clarke M, Gatzemeier W et al; Systemic therapy for treating locoregional recurrence in women with breast cancer.

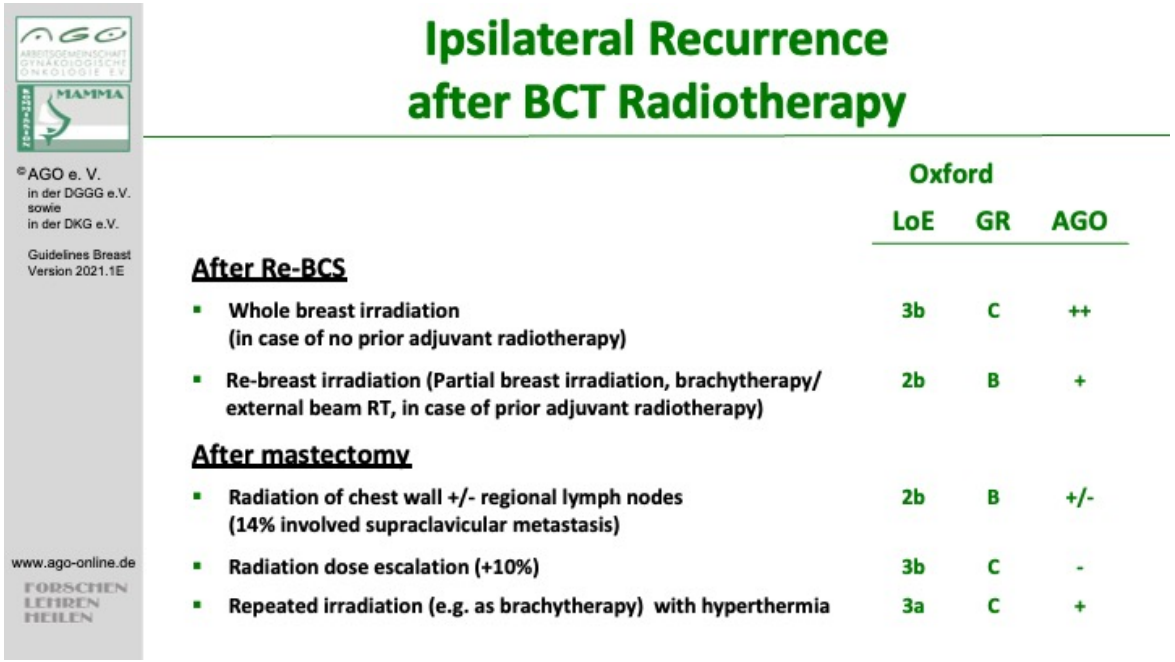
Cochrane Database Syst Rev. 2001;(4)
5. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. NCCN Guidelines (National Comprehensive Cancer Network, 2019); https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf, Version 3.2019 — September 6, 2019 (download 25. Jan. 2020
7. F. Cardoso ,A. Costa , E. Senkus et al; 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259

Statement: Trastuzumab based therapy in HER-2 overexpressing tumors

1. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.2 Aktualisierung August 2019, AWMF-Register-Nummer: 032 – 045OL; https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.2/LL_Mammakarzinom_Langversion_4.2.pdf

Statement: Checkpoint-Inhibitoren bei PD-L1 Überexpression

1. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Cortes J, Cescon DW, Rugo HS et al; KEYNOTE-355 Investigators.Lancet. 2020 Dec 5;396(10265):1817-1828.



Ipsilateral Recurrence after BCT Radiotherapy

	Oxford LoE	Oxford GR	Oxford 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	+

Statement: Whole breast radiation

1. McCready DR, Fish EB, Hiraki GY et al; Total mastectomy is not always mandatory for the treatment of recurrent breast cancer after lumpectomy alone. Can J Surg 35(5):485 :485-8, 1992
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.2 Aktualisierung August 2019, AWMF-Register-Nummer: 032 – 045OL; https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.2/LL_Mammakarzinom_Langversion_4.2.pdf (download 25.Jan 2020)
3. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
4. Skinner HD, Strom EA Motwani SB et al; Radiation dose escalation for locoregional recurrence of breast cancer after mastectomy. Radiat Oncol 8: 13, 2013

Statement: Re-irradiation (breast)

1. Hannoun-Levi JM et al; Partial breast irradiation as second conservative treatment for local breast cancer recurrence. Int J Radiat Oncol Biol Phys 60(5):1385-92, 2004
2. Kuerer HM; Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast

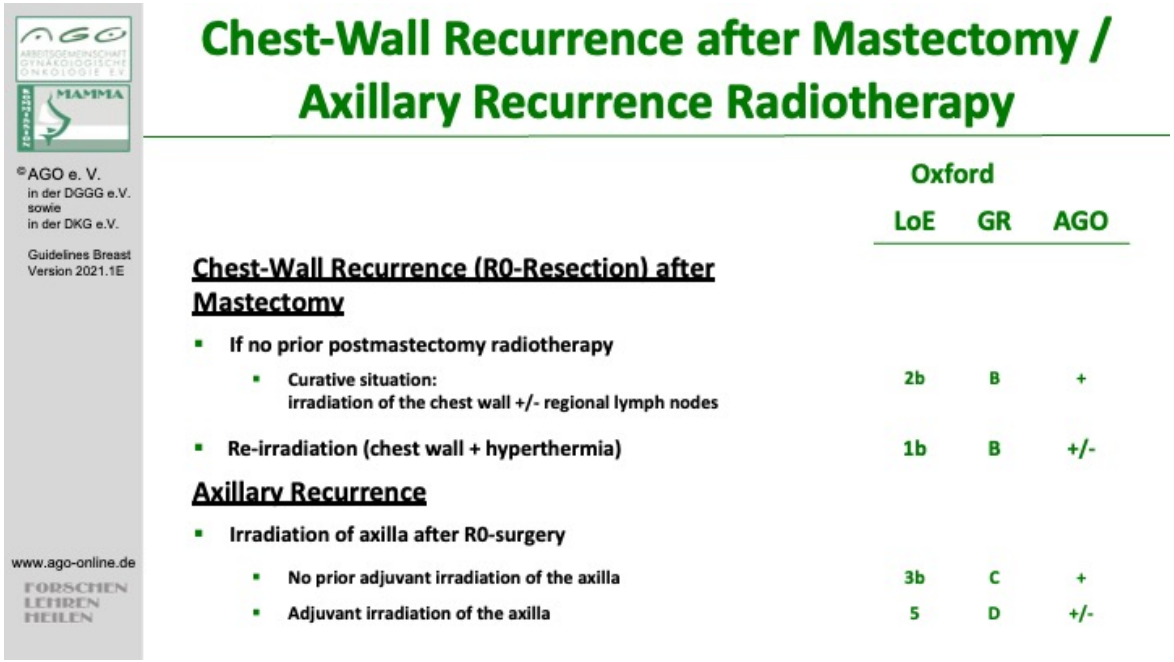
irradiation. Cancer 100(11):2269-80, 2004
3. Alpert TE, Kuerer HM, Arthur DW et al; Ipsilateral breast tumor recurrence after breast conservation therapy: outcomesof salvage mastectomy vs. salvage breast-conserving surgery and prognosticfactors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
4. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
5. Skinner HD, Strom EA, Motwani SB et al; Radiation dose escalation for locoregional recurrence of breast cancer after mastectomy. Radiat Oncol 8: 13, 2013
6. Linthorst M, van Geel AN, Baaijens M et al; Re-irradiation and hyperthermia after pulsed dose rate (PDR) brachytherapy moulds for breast cancer local recurrences. Int J Radiat
7. Surgery for recurrent breast cancer . Radiother Oncol 2013;109:188-93
8. Linthorst M, van Geel AN, Baartman EA et al; Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. Strahlenther Onkol 2013;189:387-393
9. Datta NR et al; Hyperthermia and radiation therapy in locoregional recurrent breast cancer: A systematic review and metaanalysis. Int J Rad Oncol 94:1073-87 (2016)
10. Sellam Y, Shahadi ID, Gelernter I et al; Local recurrence of breast cancer: Salvage lumpectomy as an option for local treatment. Breast J. 2019 Jul;25(4):619-624. doi: 10.1111/tbj.13290
11. Forster T, Akbaba S, Schmitt D et al; Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation. J Contemp Brachytherapy. 2019 Aug;11(4):312-319. doi: 10.5114/jcb.2019.87001
12. Cozzi S, Jamal DN, Slocker A et al; Second breast-conserving therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor recurrence: a retrospective study of 40 patients. J Contemp Brachytherapy. 2019 Apr;11(2):101-107. doi: 10.5114/jcb.2019.84689
13. Hannoun-Levi JM, Gal J, Van Limbergen E, et al.: Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database. Int J Radiat Oncol Biol Phys. 2020 Dec 29:S0360-3016(20)34722-2. doi: 10.1016/j.ijrobp.2020.12.029.

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

1. Wahl AO, Rademaker A, Kiel KD et al; Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. Int J Radiat Oncol Biol Phys. 2007 Sep 13

Statement Re-Irradiation of the chest wall with hyperthermia

1. Auoragh A, Strnad V, Ott OJ et al; Re-irradiation of the chest wall for local breast cancer recurrence : Results of salvage brachytherapy with hyperthermia. Strahlenther Onkol. 2016 Sep;192(9):617-23.
2. Datta NR, Puric E, Klingbiel D et al; Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1073-87.
3. Oldenborg S, Valk C, van Os R et al; Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016
4. Oldenborg S, et al., Re-Irradiation und hyperthermia for recurrent breast cancer encuirasse. Strahlentherapie und Onkologie 194: 206-214, 2018



Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy

	Oxford LoE	Oxford GR	Oxford 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	+/-

Statement: If no prior postmastectomy radiotherapy

1. Wahl AO, Rademaker A, Kiel KD et al; Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. Int J Radiat Oncol Biol Phys 70(2):477-84, 2008

Statement: Re-irradiation (chest wall + hyperthermia)

1. Zagar TM, Oleson JR, Vujaskovic Z et al; Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: a review of the randomised data. Int J Hyperthermia 26(7):612-7, 2010
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Statement Axillary recurrence

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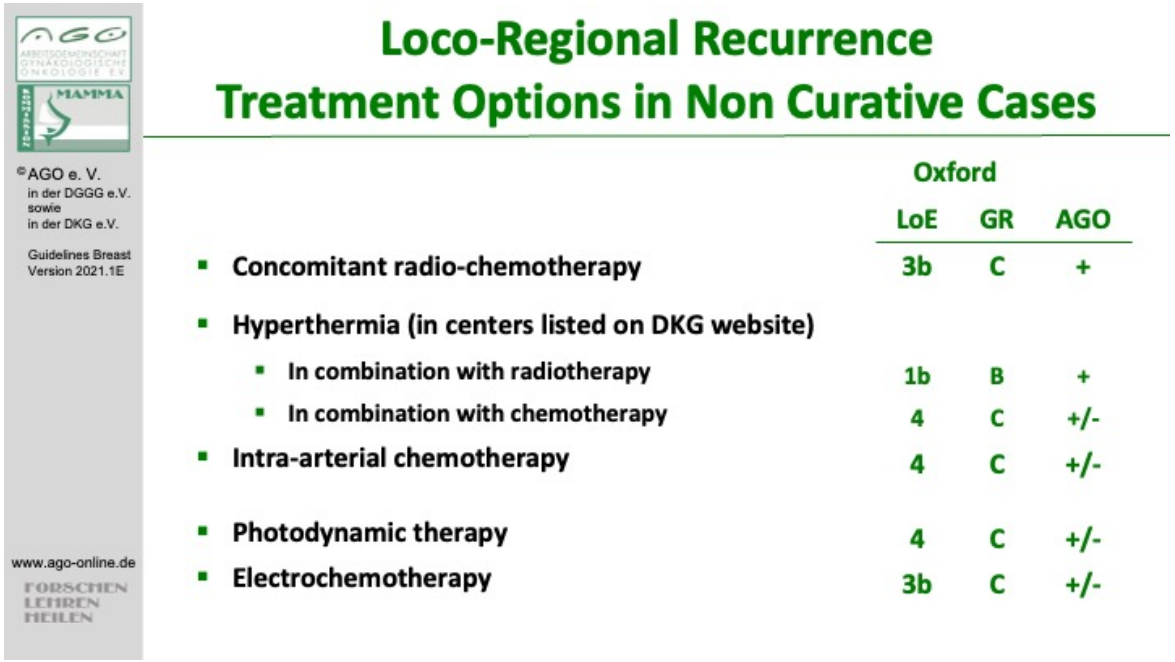

Statement: Concomitant radio-chemotherapy

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Statement: Hyperthermia + radiotherapy +/- chemotherapy

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Statement: Intraarterial chemotherapy

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Statement: Photodynamic therapy

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