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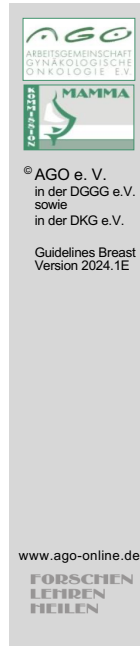
Guidelines Breast
Version 2024.1E

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Loco-Regional Recurrence



Loco-Regional Recurrence

- **Versions 2002–2023:**
**Audretsch / Bauerfeind / Blohmer/ Brunnert / Budach /
Costa / Dall / Ditsch/ Fehm / Fersis / Friedrich / Harbeck / Heil /
Gerber / Gluz / Göhring / Hanf / Kühn/ Lisboa / Lux / Maass /
Mundhenke / Rezai / Rody / Simon / Solbach / Solomayer /
Souchon / Thomssen / Wenz / Wöckel**
- **Version 2024:**
Dall / Kühn

Screened data bases


Pubmed 2005 - 2023, ASCO 2005 – 2023, SABCS 2009 – 2023, Cochrane data base

Guidelines

1. F. Cardoso ,A. Costa , E. Senkus et al; 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259
2. Cardoso F, Costa A, Norton L et al; ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014 Oct;23(5):489-502.
3. Lin NU, Thomssen C, Cardoso F et al; European School of Oncology-Metastatic Breast Cancer Task Force. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013 Jun;22(3):203-10.
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)
5. 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 (letzter Zugriff 25.01.2020)

6. Harms W, Budach W, Dunst J et al; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther Onkol. 2016 Apr;192(4):199-208.

<div>  <h2>Loco-Regional Recurrence Incidence and Prognosis</h2> </div>		
<div> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div>		
Localization	10-y. incidence (%)	5-y. Overall Survival (%)
Ipsilateral recurrence ¹ (post BEO + irradiation)	10 (2–20)	65 (45–79)
Chest wall ¹ (post mastectomy)	4 (2–20)	50 (24–78)
As above plus supraclavicular fossa ² Axilla:	34	49 (3-y. OS)
After ALND ¹	1 (0.1–8)	55 (31–77)
After SLNE ⁴	1	93
Multiple localizations ²	16 (8–19)	21 (18–23)
<p>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</p>		

1. Haffty BG, Fischer D, Beinfeld M et al; Prognosis following local recurrence in the conservatively treated breast cancer patient. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991
2. Reddy JP, Levy L, Oh JL et al; Long-term outcomes in patients with isolated supraclavicular nodal recurrence after mastectomy and doxorubicin-based chemotherapy for breast cancer. Int J Radiat Oncol Biol Phys 80(5):1453-7, 2011
3. Karabali-Dalamaga S., Souhami R. L., O'Higgins N. J. et al; Natural history and prognosis of recurrent breast cancer. Br Med J 2(6139):730-733, 1978
4. Andersson Y, de Boniface J, Jönsson PE et al; Swedish Breast Cancer Group; Swedish Society of Breast Surgeons. Axillary recurrence rate 5 years after negative sentinel node biopsy for breast cancer. Br J Surg 99(2):226-31, 2012
5. Lowery AJ, Kell MR, Glynn RW et al; Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012 Jun;133(3):831-41. www.tumorregister-muenchen.de
6. Neuman HB, Schumacher JR, Francescatti AB et al. Alliance/American College of Surgeons Clinical Research Program Cancer Care Delivery Research Breast Cancer Surveillance Working Group. Risk of Synchronous Distant Recurrence at Time of Locoregional Recurrence in Patients With Stage II and III Breast Cancer (AFT-01). J Clin Oncol. 2018;36(10):975-980.
7. Holleczer B, Stegmaier C, Radosa JC et al. Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis - results from a registry-based study from Germany. BMC Cancer. 2019 May

30;19(1):520.

8. https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.4/LL_Mammakarzinom_Langversion_4.04.pdf (8.1.2021)

Loco-Regional Recurrence Staging

Examinations before treatment

- Tissue biopsy
- Re-assessment of ER, PR, HER2
- Complete re-staging (slice imaging*)
- „Liquid biopsy“

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

* Standard: CT thorax / abdomen / pelvis and bone scan, in certain cases whole body MRI or ¹⁸F FDG PET-CT may be used

1. Veronesi U, Marubini E, Del Vecchio M et al; Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. J Natl Cancer Inst 87(1):19-27, 1995
2. Hölzel D, Engel L, Schmidt M et al; Modell zur primären und sekundären Metastasierung beim Mammakarzinom und dessen klinische Bedeutung. Strahlenther Onkol 177:10-24, 2001
3. Tennant S, Evans A, Macmillan D et al; CT staging of loco-regional breast cancer recurrence. A worthwhile practice? Clin Radiol. Sep;64(9):885-90, 2009
4. F. Cardoso ,A. Costa , E. Senkus et al; 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259
5. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5) Ann Oncol 2020 Dec;31(12):1623-1649
6. Sacchini V. Restaging Patients With Locoregional Relapse: Is There Any Benefit? : Commentary on "Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations?" by Elfgen, Constanze et al. Ann Surg Oncol. 2019;26(11):3415-3417.
7. Poodt IGM, Schipper RJ, de Greef BTA et al., Sentinel Node And Recurrent Breast Cancer (SNARB) Research Group. Screening for distant metastases in patients with ipsilateral breast tumor recurrence: the impact of different imaging modalities on distant recurrence-free interval. Breast Cancer Res Treat. 2019;175(2):419-428.
8. Elfgen C, Schmid SM, Tausch CJ, et al. Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local

and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations? Ann Surg Oncol. 2019 Oct;26(11):3455-3461.

9. Hyland CJ, Varghese F, Yau C, et al. Use of 18F-FDG PET/CT as an Initial Staging Procedure for Stage II-III Breast Cancer: A Multicenter Value Analysis. J Natl Compr Canc Netw. 2020 Nov 2;18(11):1510-1517
10. Ko H, Baghdadi Y, Love C, et al. Clinical Utility of 18F-FDG PET/CT in Staging Localized Breast Cancer Before Initiating Preoperative Systemic Therapy. J Natl Compr Canc Netw. 2020 Sep;18(9):1240-1246

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	
▪ Inappropriate systemic treatment at first recurrence	3b	C	
<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	
▪ LVI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
<u>Predictive factors for treatment considerations</u>			
▪ HER2	2b	B	++
▪ ER and PR	2b	B	++

* Risk factors for local relapse see chapter "prognostic factors"

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
2. Lannin DR, Haffty BG; End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

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

1. Cheng SH, Horng CF, Clarke JL et al; Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. Int J Radiat Oncol Biol Phys 64(5):1401-9, 2006
2. Lannin DR, Haffty BG; End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

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

1. Lee JS, Kim SI, Park HS et al; The impact of local and regional recurrence on distant metastasis and survival in patients treated with BCT. J Breast Cancer 14:191-7, 2011
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, Beinfeld 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

Ipsilateral Locoregional Recurrence Surgical Treatment

	Oxford		
	LoE	GR	AGO
▪ After mastectomy: wide exzision (aim R0)	3b	B	++
▪ After BCS:			
▪ 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	+/-
▪ rcN0:			
▪ Axillary intervention after prior AxDis	4	C	-
▪ Re-SLNE after prior SLNE	2a	B	-
▪ in histologically confirmed axillary recurrence: Excision with clear margins	5	C	+
▪ Palliative surgery in M1-situation or R0 not achievable (e.g. pain, ulceration, psychosocial indication)	5	D	+

* After consideration of risk factors for repeated relapse (time from primary diagnosis, tumor size)

Statement: Mastectomy (aim: R0); Re-BET +/- Radiation)

1. Alpert TE, Kuerer HM, Arthur DW et al; Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors 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-conserving treatment 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 Guidelines (National Comprehensive Cancer Network, 2022); https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf, Version 8.2021 — September 13, 2021 (download 02.01.2021)
5. Bottero M, Borzillo V, Pergolizzi S et al; The Italian Association of Radiotherapy and Oncology Recommendation for Breast Tumor Recurrence: Grades of Recommendation, Assessment, Development and Evaluation Criteria, J Breast Cancer. 2021 Jun;24(3):241-252. doi: 10.4048/jbc.2021.24.e27. Epub 2021 May 13.
6. Gentilini O, Botteri E, Veronesi P et al., Repeating conservative surgery after ipsilateral breast tumor reappearance: criteria for selecting the best candidates Ann Surg Oncol 2012 Nov;19(12):3771-6.

Statement: Axillary intervention (SNE/AxDiss) after prior SNB / Re-SNB after SNB / (Re-)ALND bei rcN+

1. Intra M, Trifirò G, 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.
12. Intra M, Viale G, Vila J, et al. Second axillary sentinel lymph node biopsy for breast tumor recurrence: experience of the European Institute of Oncology. *Ann Surg Oncol.* 2015;22:2372–7. <https://doi.org/10.1245/s10434-014-4282-5>.
13. Vicini E, Leonardi MC, Kahler Ribeiro Fontana S et al: How to Perform Repeat Sentinel Node Biopsy Safely After a Previous Mastectomy: Technical Features and Oncologic Outcomes. *Ann Surg Oncol.* 2021 Nov 8. doi: 10.1245/s10434-021-10986-z.

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



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Mastectomy vs. BCS + Partial Breast Irradiation

- 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-y-DFS, complications
- Median follow-up 75.4 months
- No differences in 5-y 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

Loco-regional Recurrence after R0-Resection - Systemic Treatment

	Oxford		
	LoE	GR	AGO
According to pathohistological re-evaluation of the recurrent tumor (ER, PR, HER2) and in consideration of time from primary diagnosis, pre-treatment, co-morbidities and patient's preference			
▪ Endocrine therapy in endocrine responsive tumors	2b	B	++
▪ Chemotherapy (consider preoperative) in case of first HR-negative relapse	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
6. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5) Ann Oncol 2020 Dec;31(12):1623-1649

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

Loco-Regional Recurrence Chemotherapy

- **CALOR Trial update (CHT vs. no CHT)**
 - n = 163 (2003 - 2010), median follow-up of 9 years, all R0 resection
 - Time interval until recurrence: 3.6 years (ER neg)
6.8 years (ER pos)
 - CHT is effective in ER neg disease (primary tumor and recurrence)
 - CHT is not effective in ER pos disease (primary tumor and recurrence)
 - The results were independent from the site of recurrence, previous chemotherapy and time interval from primary surgery

Wapnir IL et al. J Clin Oncol 2018, Vol 36, issue 2, pp 1073-1079



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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. J Clin Oncol 2018, Vol 36, issue 2, pp 1073-1079

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

	Oxford		
	LoE	GR	AGO
According to 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, 2022);
https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf, Version 8.2021 — September 13, 2021 (download 02.01.2021)
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
8. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5) Ann Oncol 2020 Dec;31(12):1623-1649
9. Gennari A , André, F, Barrios CH et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer Ann Oncol 2021 Dec 32 (12), 1475-1495

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

Resectable ipsilateral Breast Tumor Recurrence after BCS – Radiotherapy

	Oxford		
	LoE	GR	AGO
After Re-BCS			
▪ Whole breast irradiation (in case of no prior adjuvant radiotherapy)	3b	C	++
▪ Repeated (2.)-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 (in case of no prior adjuvant radiotherapy, according to risk factors)	2b	B	+
▪ Radiation dose escalation	3b	C	-
▪ Repeated (2.) irradiation			
▪ in case of R0 resection (according to risk factors)	3b	B	+/-
▪ in case of R1-resection (e.g. as brachytherapy)	3b	B	+
▪ Additional regional hyperthermia (especially for R1-resections)	2a	B	+/-

* Preoperative consultation with Radiation Oncology to determine if re-irradiation is possible.

** In Sites listed on the DKG Website

<https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtr/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html>

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 – 0450L; 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)
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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: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors 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)
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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.
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15. Montagne L, Hannoun A, Hannoun-Levi J-M: Second conservative treatment for second ipsilateral breast tumor event: A systematic

review of the different re-irradiation techniques. The Breast 49:274-280, 2020

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

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. Oldenburg S, Valk C, van Os R et al; Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016
4. Oldenburg S, et al., Re-Irradiation und hyperthermia for recurrent breast cancer encuirasse. Strahlentherapie und Onkologie 194: 206-214, 2018
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7. Kaidar-Person O, Oldenburg S, Poortmans P. Re-irradiation and Hyperthermia in Breast Cancer. Clin Oncol (R Coll Radiol). 2018 Feb;30(2):73-84.

Resectable Thoracic Wall Recurrence after Mastectomy and Axillary Recurrence – Radiotherapy

	Oxford		
	LoE	GR	AGO
<u>Thoracic wall recurrence after mastectomy</u>			
▪ No prior radiotherapy			
▪ Curative situation: Radiotherapy to the thoracic wall +/- regional nodal irradiation	2b	B	+
▪ Re-irradiation of the thoracic wall	3b	B	+/-
▪ R0-resection	3b	B	+/-
▪ R1-resection (e.g. brachytherapy)	3b	B	+
▪ Additional regional hyperthermia (especially for R1-resections)*	2a	B	+
<u>Axillary recurrence</u>			
▪ Radiotherapy to the axilla (R0-resection)			
▪ No prior radiotherapy to the axilla	3b	C	+
▪ Prior radiotherapy to the axilla	5	D	+/-

* In Sites listed on the DKG Website
<https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtrf/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html>

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
2. 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.
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irresectable recurrent breast cancer: Results in 248 patients. Radiother Oncol. 2015 Nov;117(2):217-22.

7. Kaidar-Person O, Oldenborg S, Poortmans P. Re-irradiation and Hyperthermia in Breast Cancer. Clin Oncol (R Coll Radiol). 2018 Feb;30(2):73-84.

Statement Axillary recurrence

1. 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)
2. Konkin DE, Tyldesley S, Kennecke H et al; Arch Surg. Management and outcomes of isolated axillary node recurrence in breast cancer 141(9):867-72, 2006
3. Ishitobi M, Matsushita A, T Nakayama et al; Regional lymphatic recurrence after salvage surgery for ipsilateral breast tumor recurrence of breast cancer without local treatment for regional lymphatic basin. J Surg Oncol 2014;110:265-269

Unresectable Loco-Regional Recurrence (cM0) Locoregional Treatment

	Oxford		
	LoE	GR	AGO
■ Radiotherapy with curative intent (If no prior RT given)	2b	B	++
■ Additional systemic treatment to increase the efficacy of RT	3b	C	+
■ Repeat Irradiation (if prior RT given)	3b	B	+
■ Additional regional hyperthermia*	2a	B	+
■ Intra-arterial chemotherapy	4	C	+/-
■ Electrochemotherapy	3b	C	+/-

* In Sites listed on the DKG Website

<https://www.krebsgesellschaft.de/deutsche-krebsgesellschaft-wtr/deutsche-krebsgesellschaft/ueber-uns/organisation/sektion-b-arbeitsgemeinschaften/iah.html>

Definitive radiotherapy

1. Gao RW, Park SS, Jakub JW et al (2018) Durable response of early-stage breast cancer to bilateral definitive SBRT in a medically inoperable patient. Pract Radiat Oncol 8:361–365.
2. Miljanic M, Nwachukwu C, Rahimi A (2023) Definitive ablative stereotactic partial breast irradiation in early stage inoperable breast cancer. J Cancer Res Clin Oncol 149:15553–15559.
3. Moore-Palhares D, Chen H, Khan BM et al (2023) Locoregional Ablative Radiotherapy for Breast Cancer Patients Unsuitable for Surgical Resection. Pract Radiat Oncol.
4. Shibamoto Y, Takano S, Iida M et al (2022) Definitive radiotherapy with stereotactic or IMRT boost with or without radiosensitization strategy for operable breast cancer patients who refuse surgery. J Radiat Res 63:rrac047-.
5. Zabrocka E, Polce S, Roberson JD et al (2023) Utility of Stereotactic Body Radiation Therapy (SBRT) in Establishing Local Control for Invasive Breast Cancer Patients Not Undergoing Definitive Surgery. Int J Radiat Oncol Biol Phys.

Systemic therapy to increase the efficacy of radiotherapy

1. Adams S, Chakravarthy AB, Donach M, et al (2010) Preoperative concurrent paclitaxel-radiation in locally advanced breast cancer: pathologic response correlates with five-year overall survival. Breast Cancer Research and Treatment 124:723–732.
<https://doi.org/10.1007/s10549-010-1181-8>

2. Brackstone M, Palma D, Tuck AB, et al (2017) Concurrent Neoadjuvant Chemotherapy and Radiation Therapy in Locally Advanced Breast Cancer. *International journal of radiation oncology, biology, physics* 99:769–776. <https://doi.org/10.1016/j.ijrobp.2017.06.005>
3. Bollet MA, Belin L, Reyat F, et al (2012) Preoperative radio-chemotherapy in early breast cancer patients: Long-term results of a phase II trial. *Radiother Oncol* 102:82–88. <https://doi.org/10.1016/j.radonc.2011.08.017>
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10. Woodward WA, Fang P, Arriaga L, et al (2017) A Phase 2 Study of Preoperative Capecitabine and Concomitant Radiation in Women With Advanced Breast Cancer. *International journal of radiation oncology, biology, physics* 99:777–783.

Statement: Hyperthermia + radiotherapy +/- chemotherapy

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2. Jones EL, Marks LB, Prosnitz LR; Point: Hyperthermia with radiation therapy for chest wall recurrences. *J Natl Compr Canc Netw*. 5(3):339-44, 2007
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Statement: Intraarterial chemotherapy

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Statement: Electrochemotherapy

1. Campana LG, Valpione S, Falci C et al; The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. *Breast Cancer Res Treat* 134(3):1169-78, 2012
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