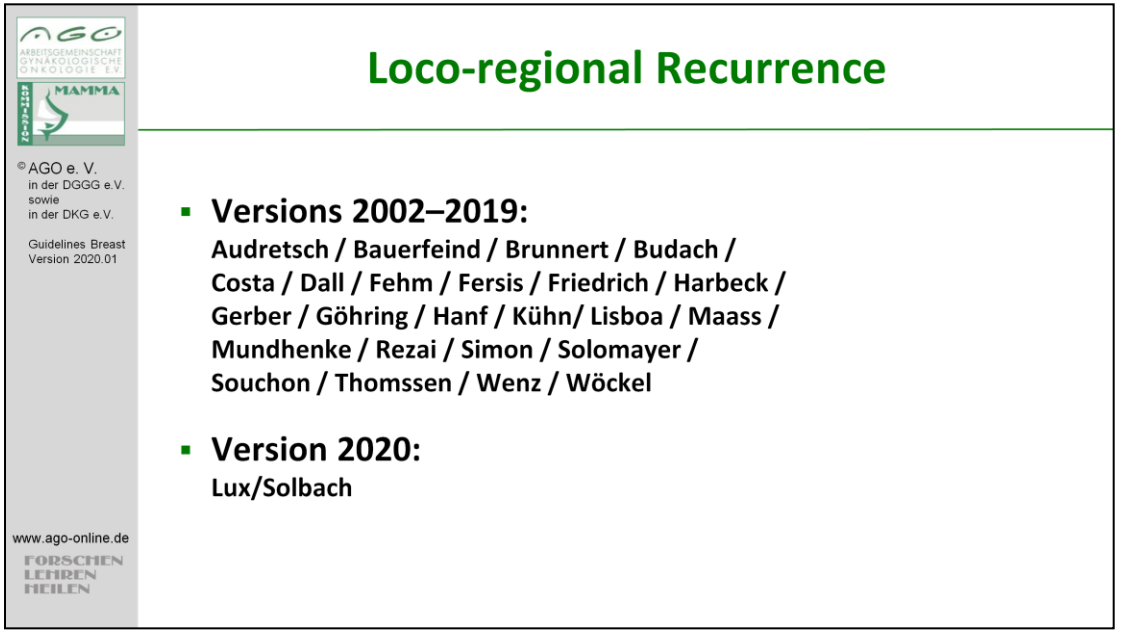
Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.01

FORSCHEN
LEHREN
HEILEN

Loco-Regional Recurrence



Screened data bases

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

Guidelines

F. Cardoso ,A. Costa , E. Senkus et al; 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259

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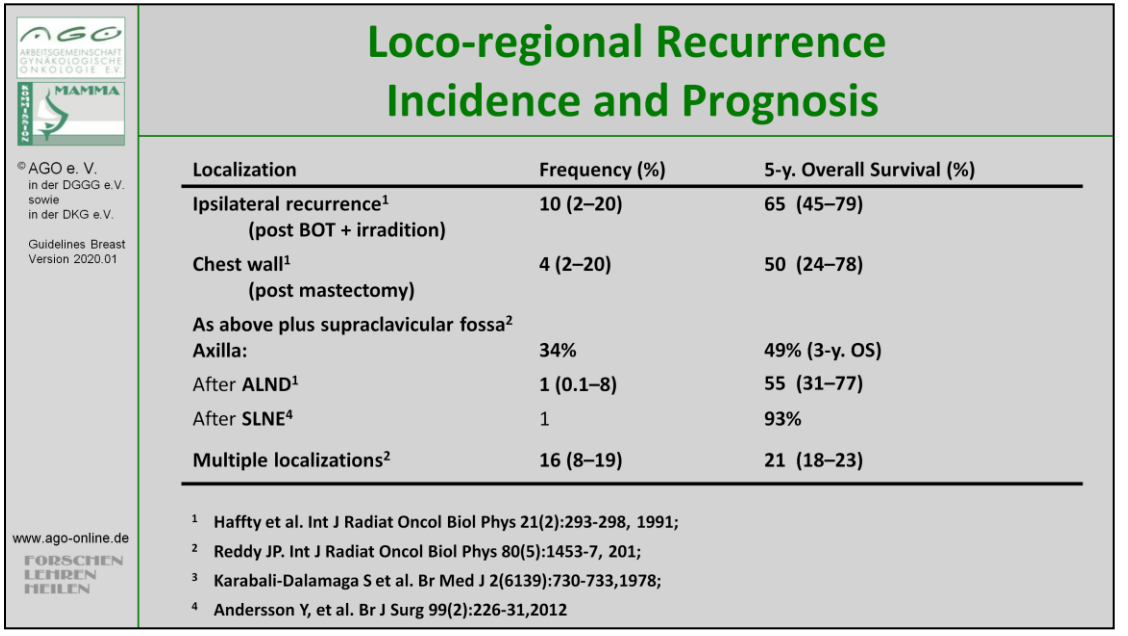
(download 25. Jan. 2020)

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)

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.



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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
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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. Holleczek B, Stegmaier C, Radosa JC et al. Risk of loco-regional recurrence and distant metastases of patients with invasive breast

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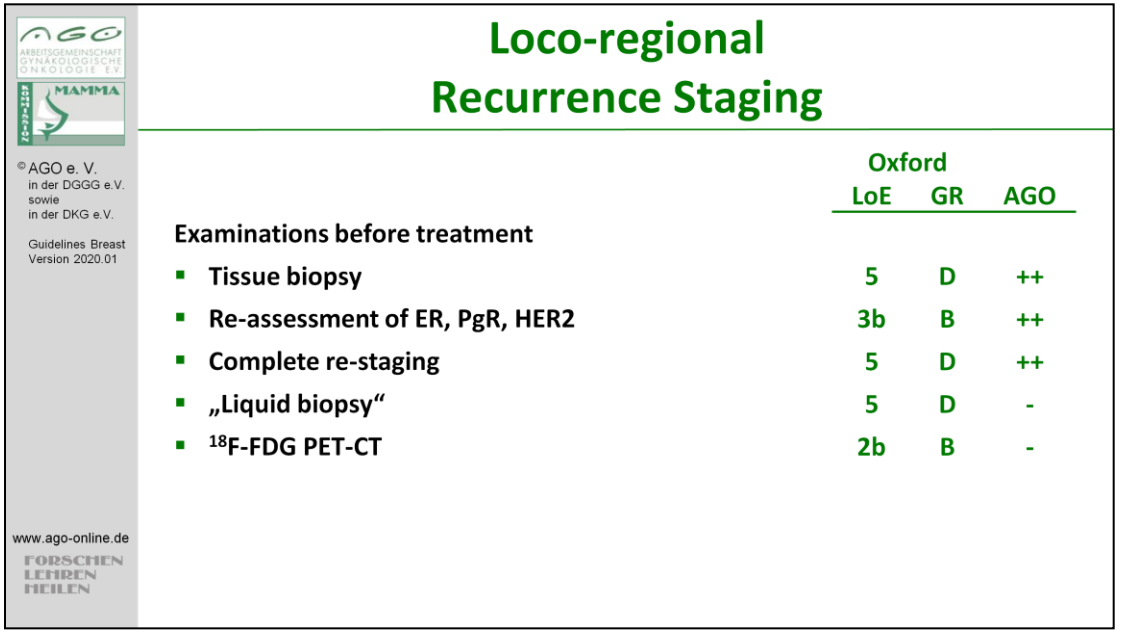

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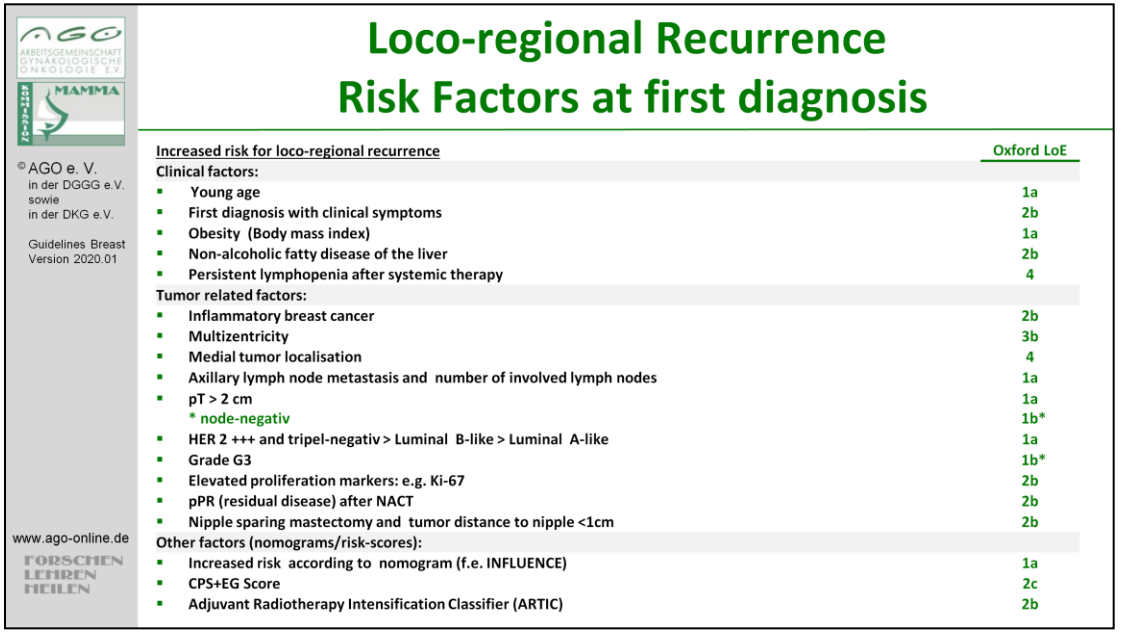
2. Hölzel D, Engel L, Schmidt M et al; Modell zur primären und sekundären Metastasierung beim Mammakarzinom und dessen klinische Bedeutung. Strahlenther Onkol 177:10-24, 2001
3. Tennant S, Evans A, Macmillan D et al; CT staging of loco-regional breast cancer recurrence. A worthwhile practice? Clin Radiol. 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. 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.
6. 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.



Informative for the whole list of factors

1. Sestak I, Dowsett M, Ferree S et al; Retrospective analysis of molecular scores for the prediction of distant recurrence according to baseline risk factors. Breast Cancer Res Treat. 2016 Aug;159(1)

Statement: Increased risk for loco-regional recurrence

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005
2. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
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5. Smith TE, Lee D, Turner BC et al; True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int J Radiat Oncol Biol Phys 48(5): 1281–1289, 2000
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9. Desai S, Hurley J et al; Impact of surgery-radiation interval on locoregional outcome in patients receiving neo-adjuvant therapy and mastectomy. Breast 19:427-30, 2013
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13. Sjöström M, Chang SL, Fishbane N et al. Clinicogenomic Radiotherapy Classifier Predicting the Need for Intensified Locoregional Treatment After Breast-Conserving Surgery for Early-Stage Breast Cancer J Clin Oncol. 201;37(35):3340-3349.

Statement: Young age

1. van der Hage JA, Mieog JS, van de Velde CJ et al; Impact of established prognostic factors and molecular subtype in very young breast cancer patients: pooled analysis of four EORTC randomized controlled trials. Breast Cancer Res 24;13(3):R68, 2011
2. Algara López M, Sanz Latiesas X, Foro Arnalot P et al; Risk factors of local relapse in breast cancer: the importance of age. Clin Transl

Oncol 9(2):110-6, 2007

3. de Bock GH, van der Hage JA, Putter H et al; Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer 42(3):351-6. 2006
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5. Elder EE, Kennedy CW, Gluch L et al; Patterns of breast cancer relapse. Eur J Surg Oncol. 32(9):922-7, 2006
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10. de Boer AZ, van der Hulst HC, de Glas NA et al. Impact of Older Age and Comorbidity on Locoregional and Distant Breast Cancer Recurrence: A Large Population-Based Study. Oncologist. 2020 Jan;25(1):e24-e30.

<u>Statement: Positive microscopic margins</u>

1. de Bock GH, van der Hage JA, Putter H et al; Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer 42(3):351-6, 2006
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for

early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005

3. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
4. Pilewskie M, Ho A, Orell E et al; Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast-conserving therapy.. Ann Surg Oncol. 2014;21(4):1209-14.
5. Bosma SC, van der Leij F, van Werkhoven E et al; Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Cancer Res Treat. 2016;156(2)
6. Dixon JM, Thomas J, Kerr GR et al; A study of margin width and local recurrence in breast conserving therapy for invasive breast cancer. Eur J Surg Oncol. 2016;42(5):657-64

Statement: Extensive intraductal component

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005
2. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213. 2003
3. Cheng SH 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

Statement: Vessel invasion

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005
2. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
3. Truong PT, Yong CM, Abnousi F et al; Lymphovascular invasion is associated with reduced locoregional control and survival in

women with node-negative breast cancer treated with mastectomy and systemic therapy. J Am Coll Surg. 200(6):912-21, 2005

4. Stuart-Harris R, Dahlstrom JE, Gupta R et al.; Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. Breast. 2019,44:153-159.
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6. Asaoka M, Narui K, Suganuma N et al. Clinical and pathological predictors of recurrence in breast cancer patients achieving pathological complete response to neoadjuvant chemotherapy.Eur J Surg Oncol. 2019:45(12):2289-2294.

Statement: ER and PR negative/ basal like or triple negative tumors /Her 2 positive tumors

1. van der Hage JA, Mieog JS, van de Velde CJ et al; Impact of established prognostic factors and molecular subtype in very young breast cancer patients:pooled analysis of four EORTC randomized controlled trials. Breast Cancer Res Breast Cancer Res 24;13(3):R68, 2011
2. Cancello G, Maisonneuve P, Rotmensz N et al; Prognosis in women with small node-negative operable breast cancer by immunohistochemically selected subtypes, Breast Cancer Res Treat 127:713-20, 2011
3. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
4. Cheng SH 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. 2006 Apr 1;64(5):1401-9
5. Dominici LS, Mittendorf EA, Wang X et al; Implications of constructed biologic subtype and its relationship to locoregional recurrence following mastectomy. Breast Cancer Res 23;14(3):R82, 2012
6. Lowery AJ, Kell MR, Glynn RW et al; Locoregional recurrence after Breast Cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 133(3):831-41, 2012
7. Wang J, Xie X et al; Locoregional and distant recurrences after breast conserving therapy in patients with triple negative breast cancer: A meta-analysis. Surg Oncol Epub ahead of print, 2013

8. Haixia Jia, Weijuan Jia, Yaping Yang et al; HER-2 positive breast cancer is associated with an increased risk of positive cavity margins after initial lumpectomy; World J Surg Oncol. 2014; 289.Published online 2014 Sep 20. doi: 10.1186/1477-7819-12-289PMCID: PMC4190445; 12: Asian Pac J Cancer Prev. 2014;15(1):315-20
9. Lai SF, Chen YH, Kuo WH et al; Locoregional Recurrence Risk for Postmastectomy Breast Cancer Patients With T1-2 and One to Three Positive Lymph Nodes Receiving Modern Systemic Treatment Without Radiotherapy. Ann Surg Oncol. 2016 Nov;23(12):3860-3869.
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11. Jwa E, Shin KH, Kim JY et al; Locoregional Recurrence by Tumor Biology in Breast Cancer Patients after Preoperative Chemotherapy and Breast Conservation Treatment. Cancer Res Treat. 2016 Oct;48(4):1363-1372. Epub 2016 Feb 18.
12. Stuart-Harris R, Dahlstrom JE, Gupta R et al.; Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. Breast. 2019;44:153-159.
13. Gabani P, Merfeld E, Srivastava AJ et al. Predictors of Locoregional Recurrence After Failure to Achieve Pathologic Complete Response to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer. J Natl Compr Canc Netw. 2019;17(4):348-356
14. Bellon JR, Guo H, Barry WT et al. Local-regional recurrence in women with small node-negative, HER2-positive breast cancer: results from a prospective multi-institutional study (the APT trial). Breast Cancer Res Treat. 2019;176(2):303-310.

Statement: Grading G3

1. de Bock GH, van der Hage JA, Putter H et al; Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer 42(3):351-6, 2006
2. 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
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4. Stuart-Harris R, Dahlstrom JE, Gupta R et al.; Recurrence in early breast cancer: Analysis of data from 3,765 Australian women

treated between 1997 and 2015. Breast. 2019;44:153-159.

Statement: pT > 2

1. Yildirim E, Berberoglu U; Local recurrence in breast carcinoma patients with T(1-2) and 1-3 positive nodes:indications for radiotherapy. Eur J Surg Oncol 33(1):28-32, 2007
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials Lancet 366: 2087–2106, 2005
3. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
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9. Livi L, Paiar F, Simontacchi G et al; Loco regional failure pattern after lumpectomy and breast irradiation in 4,185 patients with T1 and T2 breast cancer. Implications for nodal irradiation. Acta Oncol. 45: 564-70, 2006
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11. Nagao T, Kinoshita T, Tamura N et al; Locoregional recurrence risk factors and the impact of postmastectomy radiotherapy on patients with tumors 5 cm or larger.

Statement: pN (N1 vs. N0)

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005
2. www.tumorregister-muenchen.de
3. Stuart-Harris R, Dahlstrom JE, Gupta R et al.; Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. Breast. 2019;44:153-159.

Statement: pN (N1 vs. N0) and number of involved lymph nodes

1. Yildirim E, Berberoglu U; Local recurrence in breast carcinoma patients with T(1-2) and 1-3 positive nodes:indications for radiotherapy. Eur J Surg Oncol 33(1):28-32, 2007
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials Lancet 366: 2087–2106, 2005
3. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
4. Jagsi R, Raad RA, Goldberg S et al; Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. Int J Radiat Oncol Biol Phys 62(4):1035-9, 2005
5. 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
6. Truong PT, Jones SO, Kader HA et al; Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 73(2):357-64, 2009
7. Li Q, Wu S, Zhou J et al; Risk factors for locoregional recurrence after postmastectomy radiotherapy in breast cancer patients with four or more positive axillary lymph nodes. Curr Oncol. 2014 Oct;21(5):e685-90. doi: 10.3747/co.21.2000

8. Crawford JD, Ansteth M et al; Routine completion axillary lymph node dissection for positive sentinel nodes in patients undergoing mastectomy is not associated with improved local control. Am J Surg 205: 581-4, 2013

Statement: Medial tumor localisation

1. Knauerhase H, Strietzel M, Gerber B et al; Tumor location, interval between surgery and radiotherapy and boost technique influence local control after breast conserving surgery and radiation: retrospective analysis of monoinstitutional long-term results. Int J Radiat Oncol Biol Phys 72: 1048-55, 2008

Statement: elevate proliferation marker, esp. Ki67

1. Voduc KD, Cheang MC, Tyldesley S et al; Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 28(10):1684-91, 2010

Statement: Inflammatory breast cancer

1. Saigal K, Hurley J et al; Risk factors for locoregional failure in patients with inflammatory breast cancer treated with trimodality therapy. Clin Breast Cancer 13:335-43, 2013

Statement: Obesity

1. D. S. M. Chan et al; Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies Ann Oncol. Oct 2014; 25(10): 1901–1914. Published online Apr 27, 2014.
2. Xia X, Chen W, Li J et al; Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480.
3. Bergom C ,Kelly T, Bedi M et al; Association of Locoregional Control With High Body Mass Index in Women Undergoing Breast Conservation Therapy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016 Sep 1;96(1):65-71

4. Warren LE, Ligibel JA, Chen YH et al; Body Mass Index and Locoregional Recurrence in Women with Early-Stage Breast Cancer. Ann Surg Oncol. 2016 Nov;23(12):3870-3879.

Statement: Residual disease after NAC

1. Haffty BG, McCall LM, Ballman KV et al. Impact of Radiation on Locoregional Control in Women with Node-Positive Breast Cancer Treated with Neoadjuvant Chemotherapy and Axillary Lymph Node Dissection: Results from ACOSOG Z1071 Clinical Trial. Int J Radiat Oncol Biol Phys. 2019, 05(1):174-182.

Statement: Symptomatic disease

1. Stuart-Harris R, Dahlstrom JE, Gupta R et al.; Recurrence in early breast cancer: Analysis of data from 3,765 Australian women treated between 1997 and 2015. Breast. 2019;44:153-159.

Statement: Multifocality

1. Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC et al; Factors predicting local relapse and survival in patients treated with surgery for breast cancer. Asian J Surg. 2019;42(7):755-760.

Statement: Non-alcoholic fatty liver

1. Lee YS, Lee HS, Chang SW et al; Underlying nonalcoholic fatty liver disease is a significant factor for breast cancer recurrence after curative surgery. Medicine (Baltimore). 2019 Sep;98(39):e17277. doi: 10.1097/MD.0000000000017277

Statement: Nipple-Distance after NSM

1. Frey JD, Salibian AA, Lee J et al; Oncologic Trends, Outcomes, and Risk Factors for Locoregional Recurrence: An Analysis of Tumor-to-Nipple Distance and Critical Factors in Therapeutic Nipple-Sparing Mastectomy. Plast Reconstr Surg. 2019;143(6):1575-1585.
2. Wu ZY, Kim HJ, Lee JW et al. Breast Cancer Recurrence in the Nipple-Areola Complex After Nipple-Sparing Mastectomy With

Immediate Breast Reconstruction for Invasive Breast Cancer. JAMA Surg. 2019 Aug 28. doi: 10.1001/jamasurg.2019.2959.

Statement: Lymphopenia

1. Cho O, Chun M, Kim SW et al; Lymphopenia as a Potential Predictor of Ipsilateral Breast Tumor Recurrence in Early Breast Cancer. Anticancer Res. 2019;39(8):4467-4474.

Statement: Use of Nomogram/CPS+EGScore

1. Tsoutsou PG, Jeanneret Sozzi W et al; Nomograms predicting locoregional recurrence in the subtype era of breast cancer. J Clin Oncol 31: 647-8, 2013
2. Manounas EP, Anderson SJ, Dignam JJ et al; Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of NASBP B-18 and B-27. J Clin Oncol 30: 3960-6, 2012
3. Kraeima J, Siesling S, Vliegen IM et al; Individual risk profiling for breast cancer recurrence: towards tailored follow-up schemes. Br J Cancer 109: 866-71, 2013
4. Voelkel V, Draeger T, Groothuis-Oudshoorn CGM et al; Predicting the risk of locoregional recurrence after early breast cancer: an external validation of the Dutch INFLUENCE-nomogram with clinical cancer registry data from Germany. J Cancer Res Clin Oncol. 2019;145(7):1823-1833.
5. Michel LL, Sommer L, González Silos R et al. Locoregional risk assessment after neoadjuvant chemotherapy in patients with primary breast cancer: clinical utility of the CPS + EG score. Breast Cancer Res Treat. 2019;177(2):437-446.

Recent evidence for Multigene arrays predicting risk for local relapse

1. Drukker CA, Elias SG, Nijenhuis MV et al; Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.
2. Drukker CA, Elias SG, Nijenhuis MV et al; Erratum to: Gene expression profiling to predict the risk of locoregional recurrence in

breast cancer: a pooled analysis. Breast Cancer Res Treat. 2015 Jan 21.

3. Fitzal F, Filipits M, Fesl C et al; Predicting local recurrence using PAM50 in postmenopausal endocrine responsive breast cancer patients. J Clin Oncol 32:5s, 2014 (suppl; abstr 1008)
4. Bustamante Eduardo M, Popovici V, Imboden S et al; Characterization of molecular scores and gene expression signatures in primary breast cancer, local recurrences and brain metastases. BMC Cancer. 2019;19(1):549.
5. Sjöström M, Chang SL, Fishbane N et al. Clinicogenomic Radiotherapy Classifier Predicting the Need for Intensified Locoregional Treatment After Breast-Conserving Surgery for Early-Stage Breast Cancer J Clin Oncol. 2019;37(35):3340-3349.

Metaanalysis:
TNBC and Local Recurrence

Guidelines Breast
Version 2020.01

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

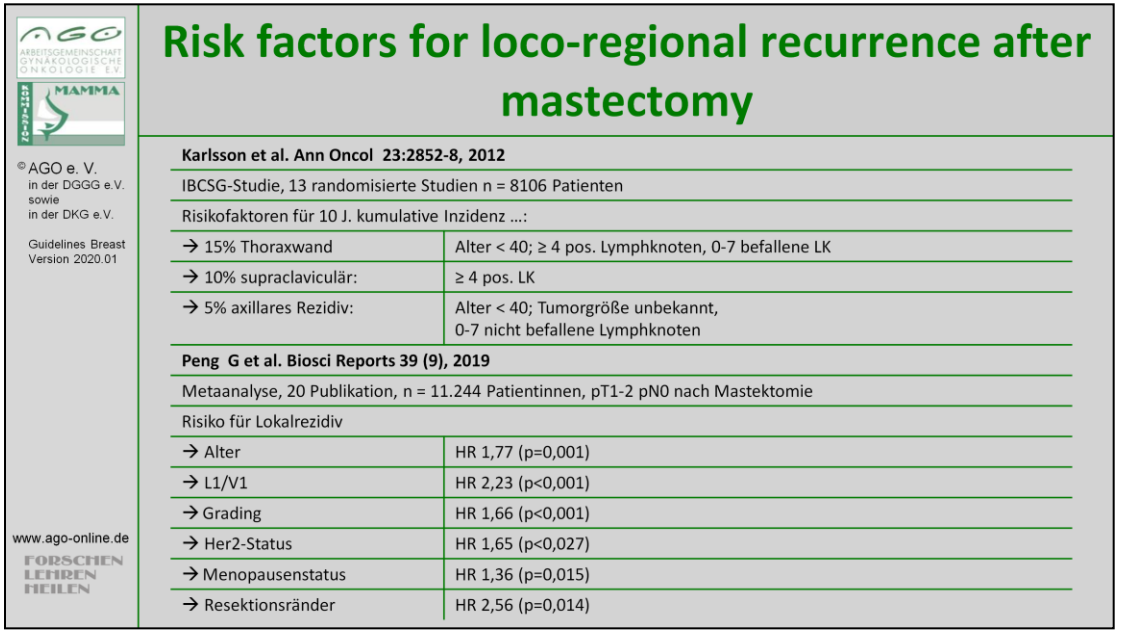
n = 15312 BC-patients, 22 studies, Hazard-ratios

BCT	**vs.**	**ME**
ILRR	**0.75 (0.65-0.87)**	
DM	**0.68 (0.60-0.76)**	

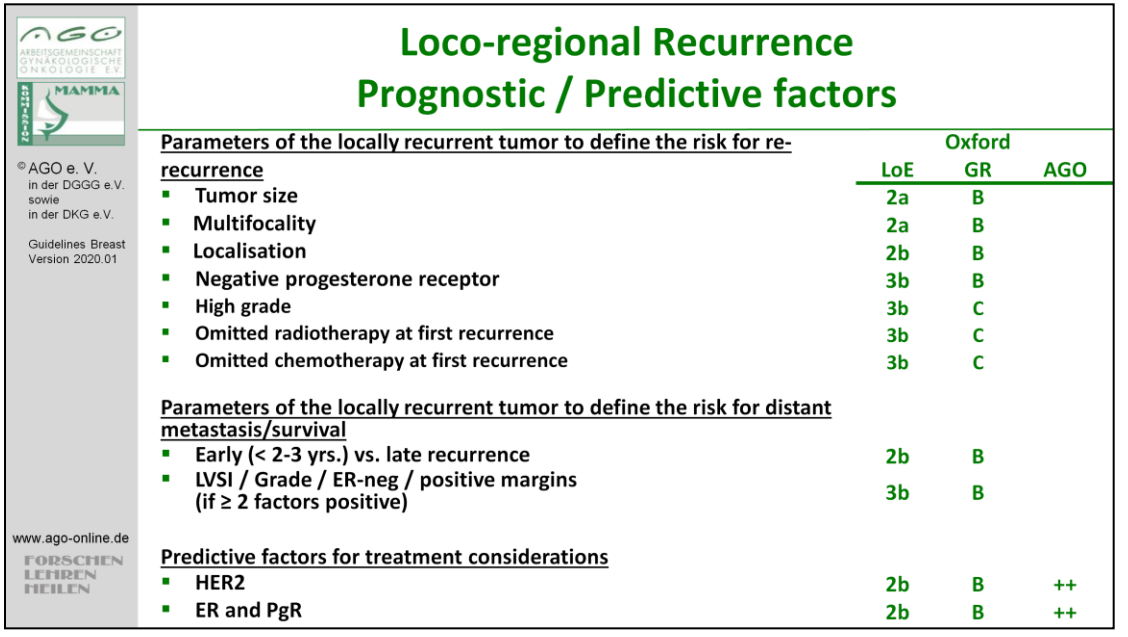
TNBC-subtype	**vs.**	**other subtype**
ILRR	**1.88 (1.58-2.22)**	
DM	**2.12 (1.72-2.62)**	

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



1. Karlsson P, Cole BF, Chua BH et al. Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report. Ann Oncol. 2012 Nov;23(11):2852-8.
2. Peng G, Zhou Z, Jiang M, Yang F. Can a subgroup at high risk for LRR be identified from T1-2 breast cancer with negative lymph nodes after mastectomy? A meta-analysis. Biosci Rep. 2019;39(9).



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, 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

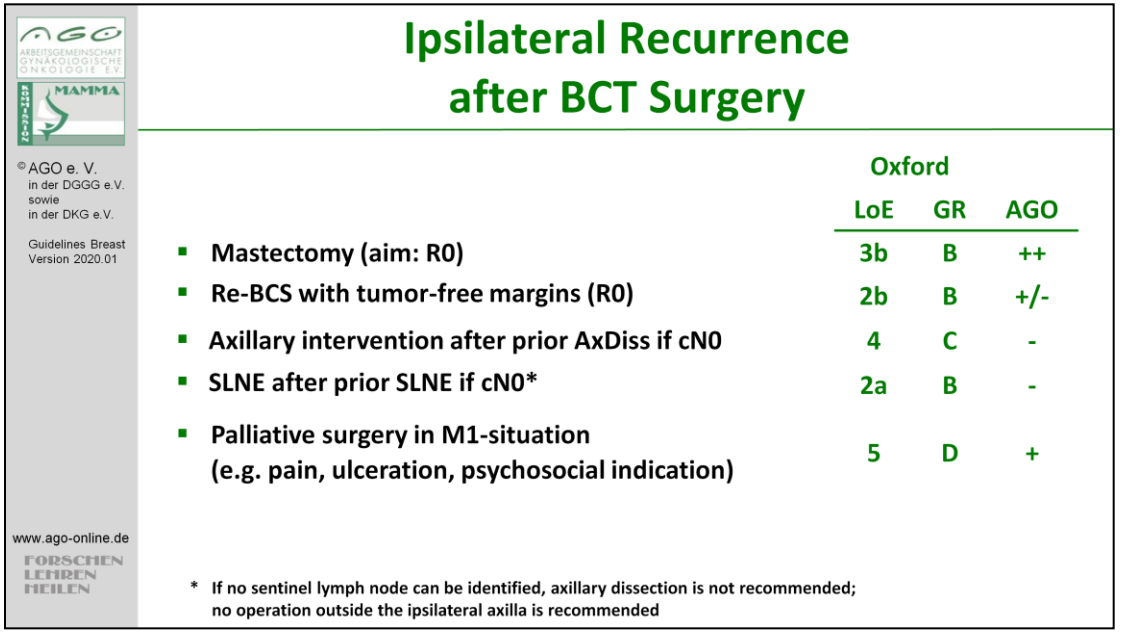
Clinicopathological Factors of the Recurrent Tumor to Predict Outcome in Patients with Ipsilateral Breast Tumor Recurrence

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:

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.

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

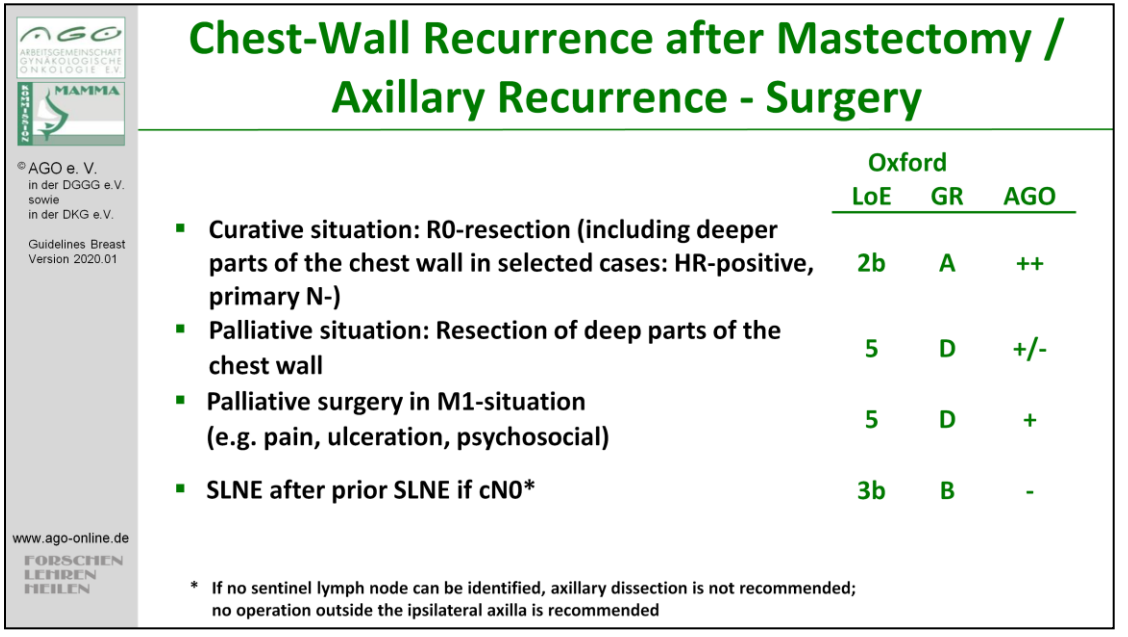
1. Intra M, TrifiròG, Viale G et al; Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 12(11):895- 899, 2005
2. Taback B, Nguyen P, Hansen N et al; Sentinel lymph node biopsy for local recurrence of breast cancer after 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



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

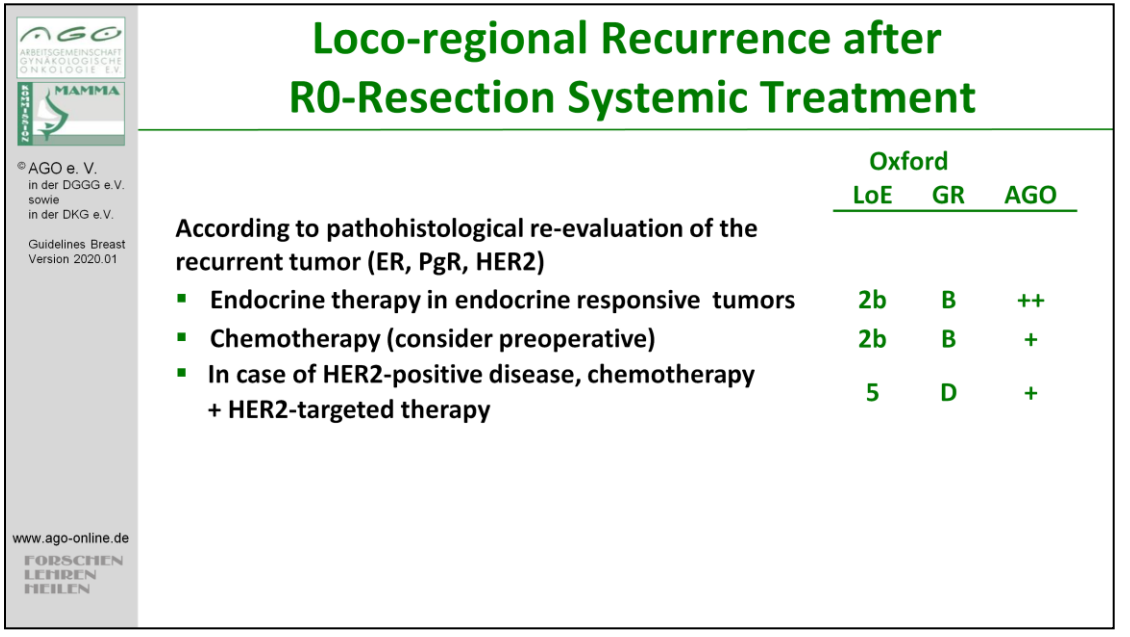
1. Mignano JE, Gage I, Piantadosi S et al; Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treatedwithout postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007
2. Pfannschmidt J, Geisbüsch P, Muley T et al; Surgical resection of secondary chest wall tumors. Thorac 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.



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

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

Guidelines Breast
Version 2020.01

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 ($p_{interaction}$=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

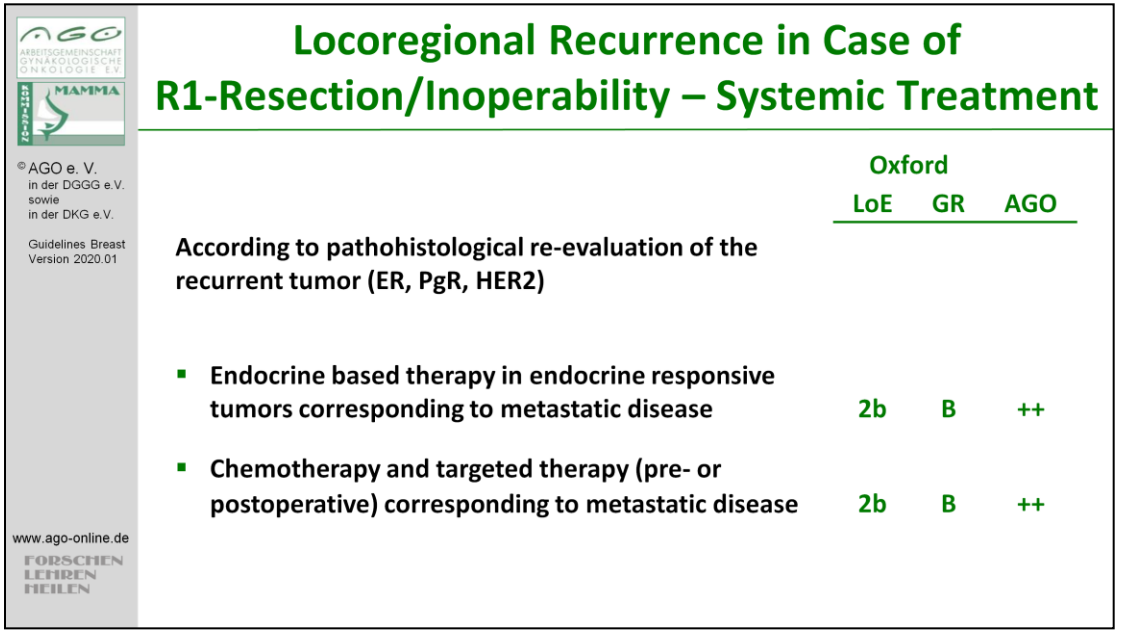
Guidelines Breast
Version 2020.01

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| Cite as



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

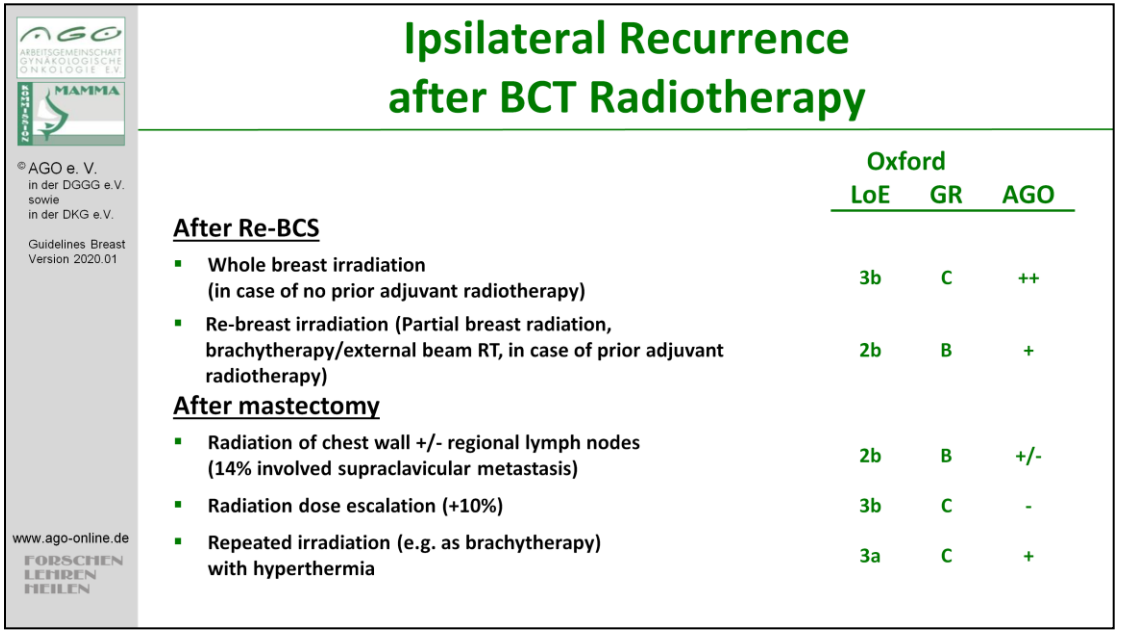
Statement: Chemotherapy (pre- or postoperatively)

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: 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

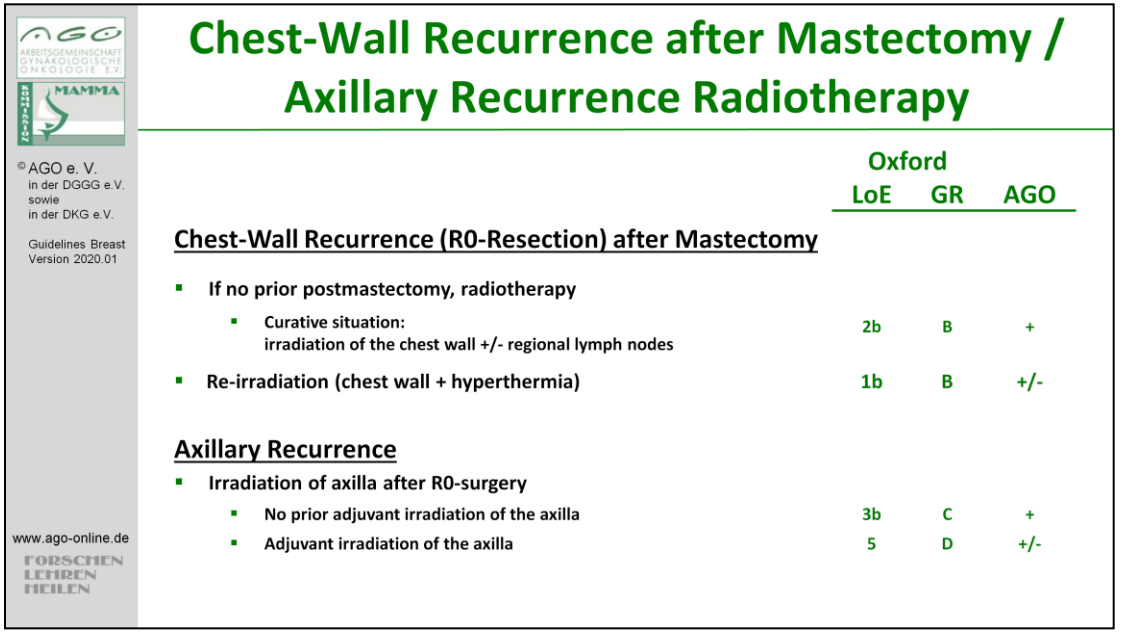
Statement: Curative situation: irradiation of the chest wall +/- regional lymph nodes

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. 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



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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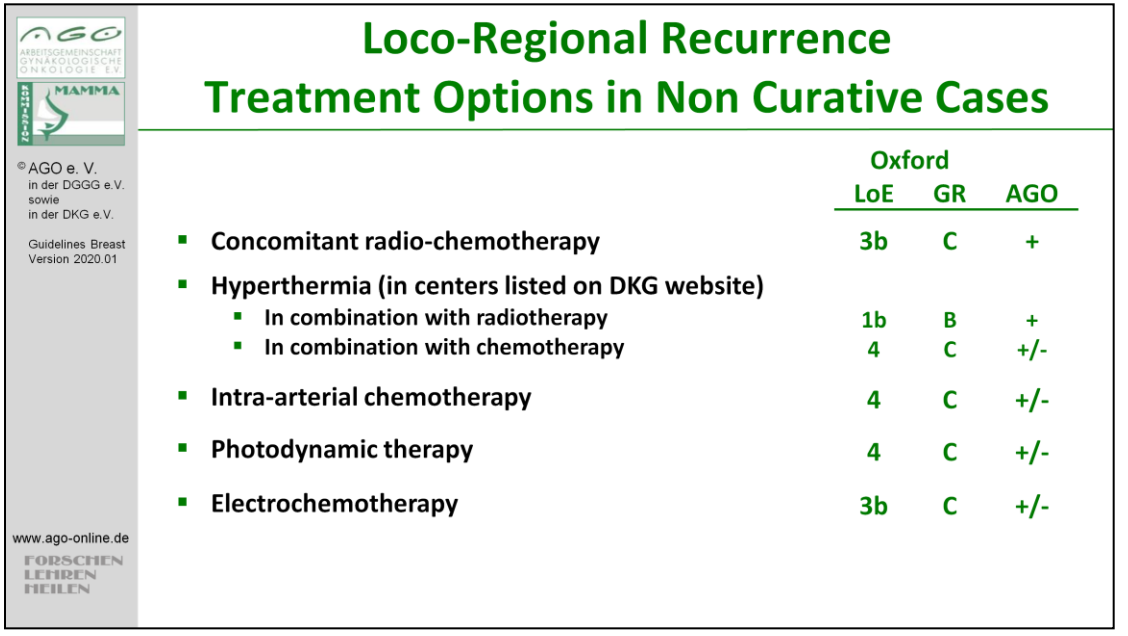

Loco-Regional Recurrence
Treatment Options in Non Curative Cases

	Oxford LoE	Oxford GR	Oxford 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	+/-

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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Statement: Electrochemotherapy

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