Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2022.1E

Loco-Regional Recurrence

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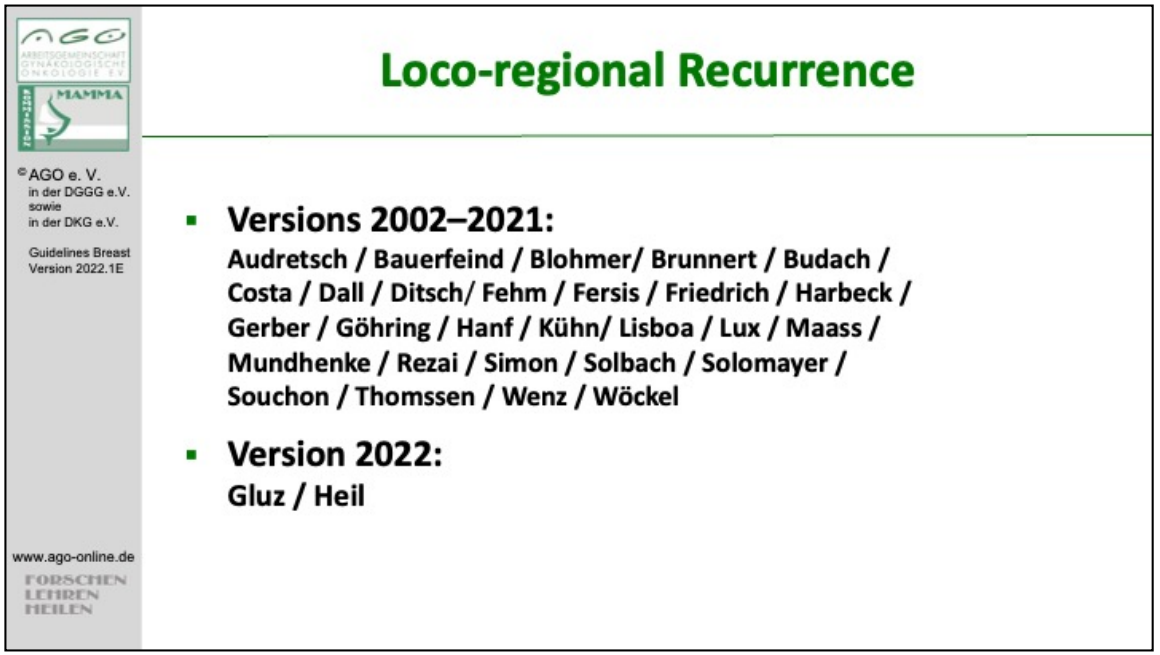

Screened data bases

Pubmed 2005 - 2021, ASCO 2005 – 2021, SABCS 2009 – 2021, Cochrane data base

Guidelines

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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.
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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

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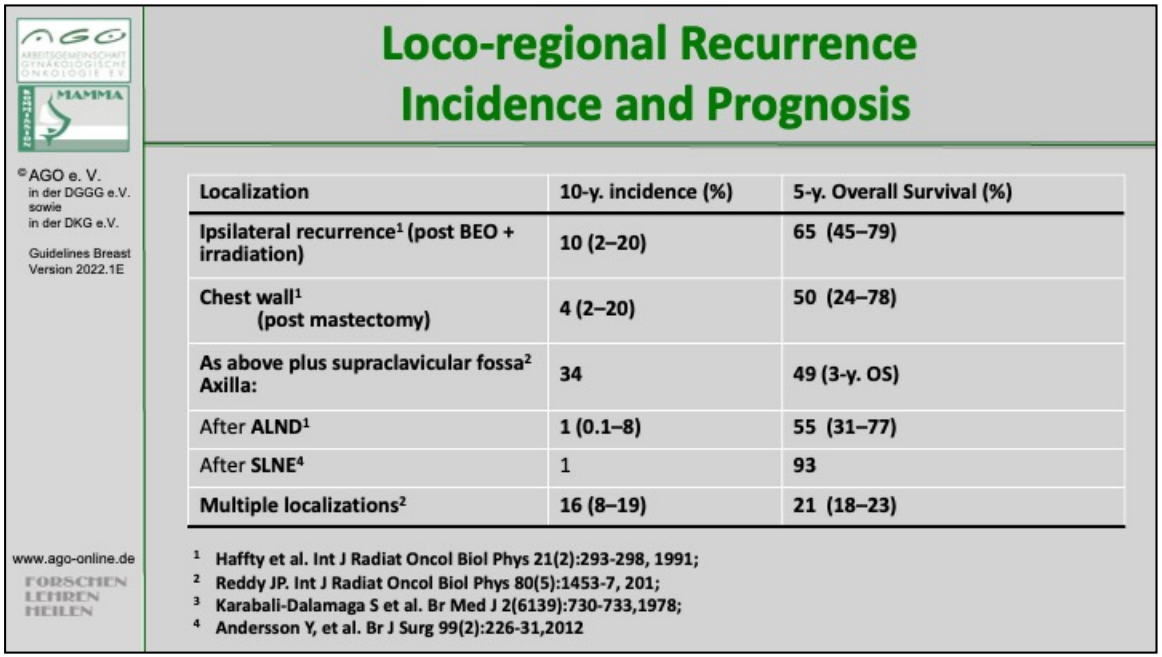

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4. Andersson Y, de Boniface J, Jönsson PE et al; Swedish Breast Cancer Group; Swedish Society of Breast Surgeons. Axillary recurrence rate 5 years after negative sentinel node biopsy for breast cancer. Br J Surg 99(2):226-31, 2012
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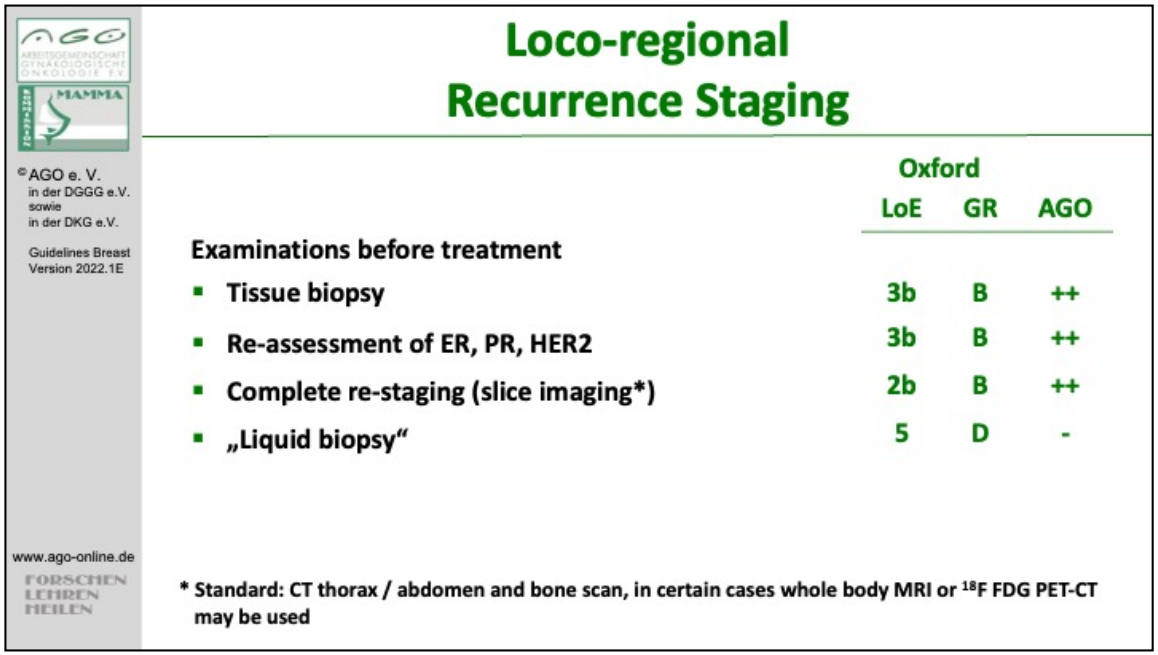

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2. Hölzel D, Engel L, Schmidt M et al; Modell zur primären und sekundären Metastasierung beim Mammakarzinom und dessen klinische Bedeutung. Strahlenther Onkol 177:10-24, 2001
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4. F. Cardoso ,A. Costa , 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.
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and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations? Ann Surg Oncol. 2019 Oct;26(11):3455-3461.
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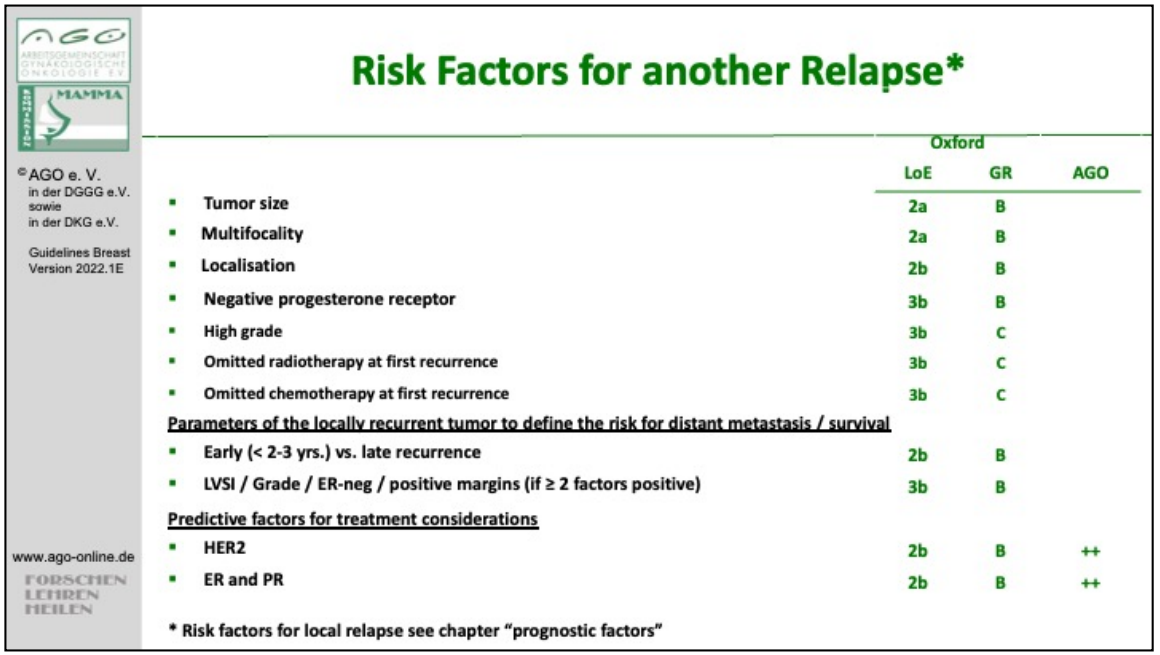
10. Ko H, Baghdadi Y, Love C, et al. Clinical Utility of 18F-FDG PET/CT in Staging Localized Breast Cancer Before Initiating Preoperative Systemic Therapy. J Natl Compr Canc Netw. 2020 Sep;18(9):1240-1246



Risk Factors for another Relapse*

	Oxford LoE	Oxford 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	++

* 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.

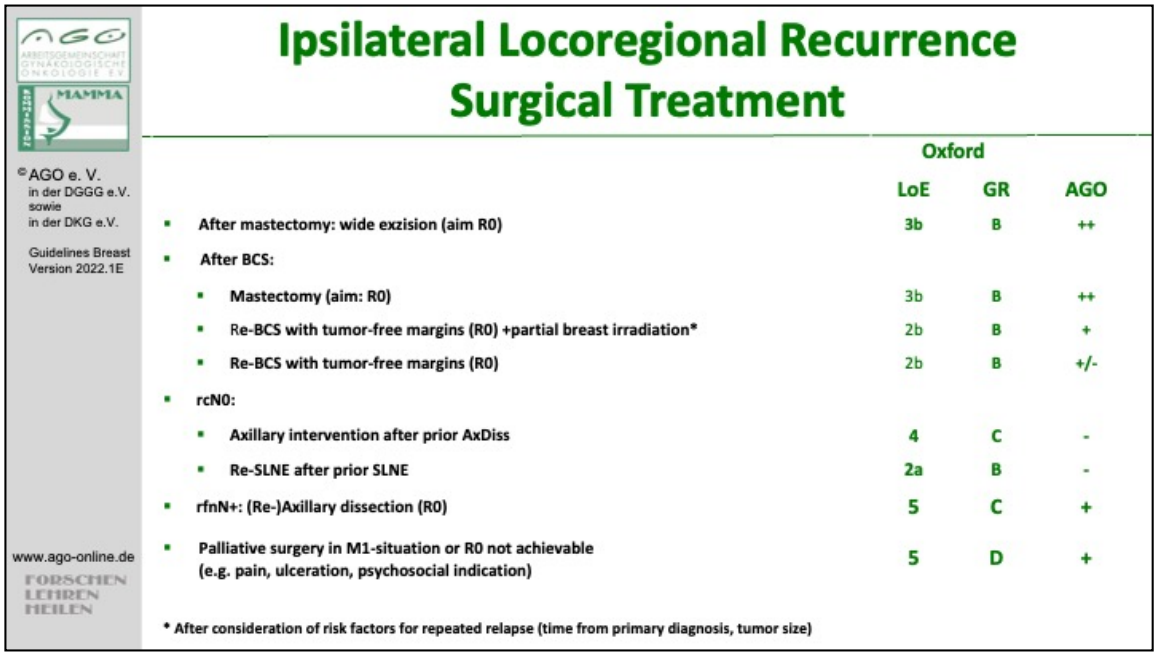
Predictive factors for treatment considerations

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, 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



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

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 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, 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.
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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.

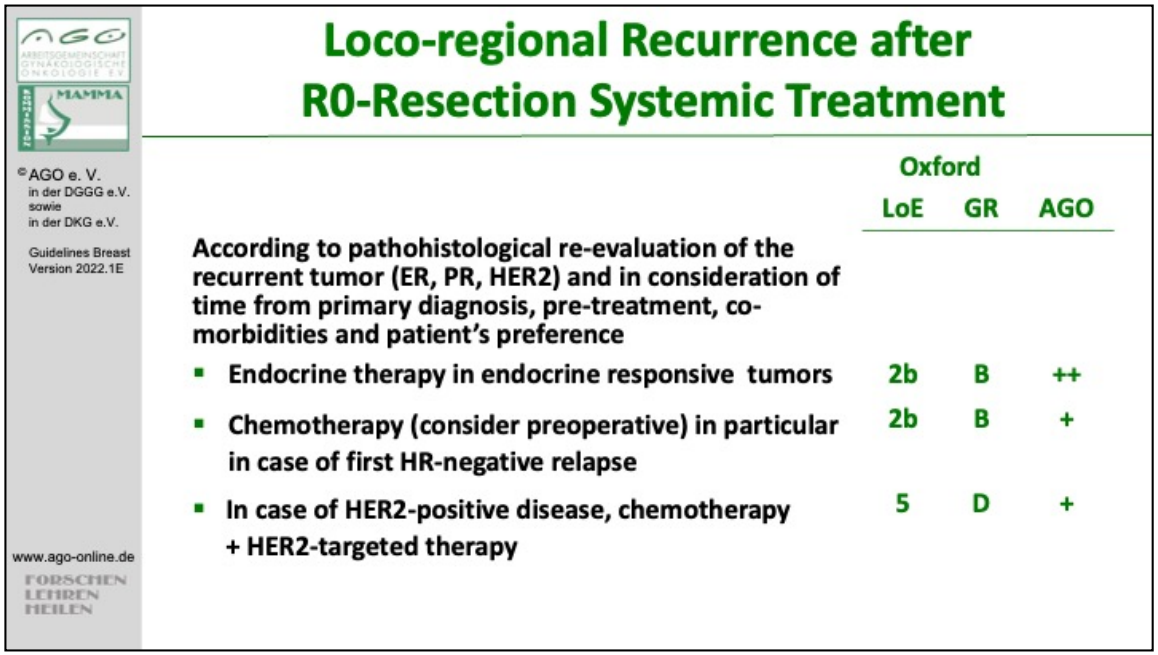
Statement: Palliative surgery in M1-situation

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

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



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

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Locoregional Recurrence Chemotherapy

- **CALOR Trial update**
  - **n = 163 (2003–2010), median follow-up of 4.9 years, all R0 resection**
  - **5-y DFS: 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

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

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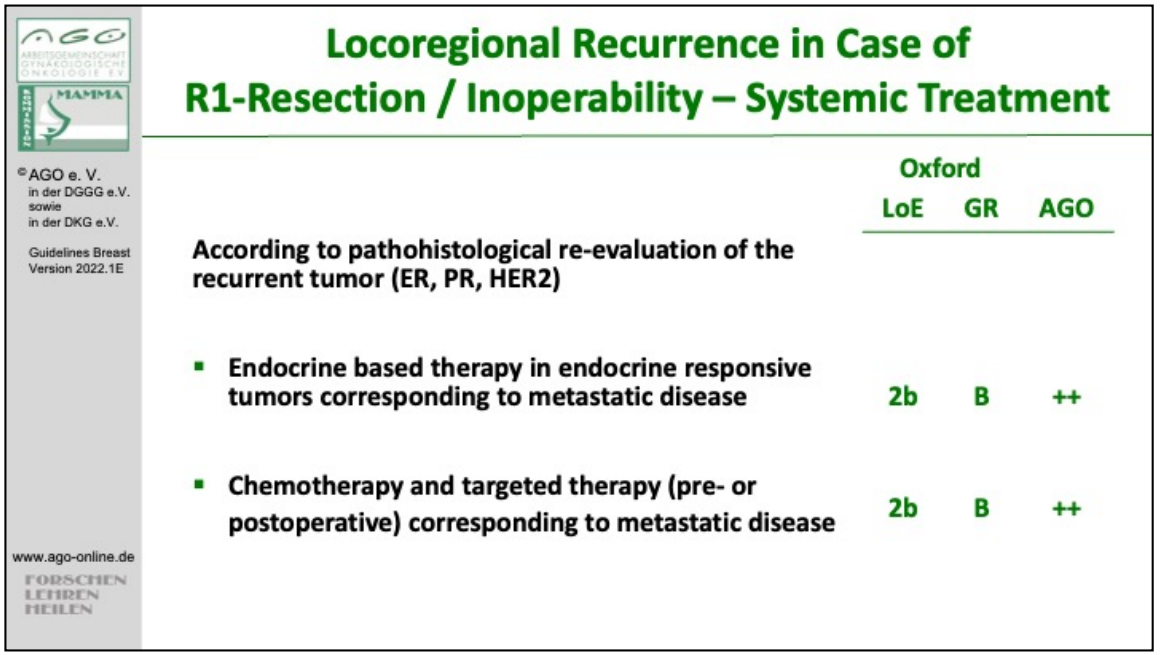


Statement: Endocrine therapy in endocrine responsive disease

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.

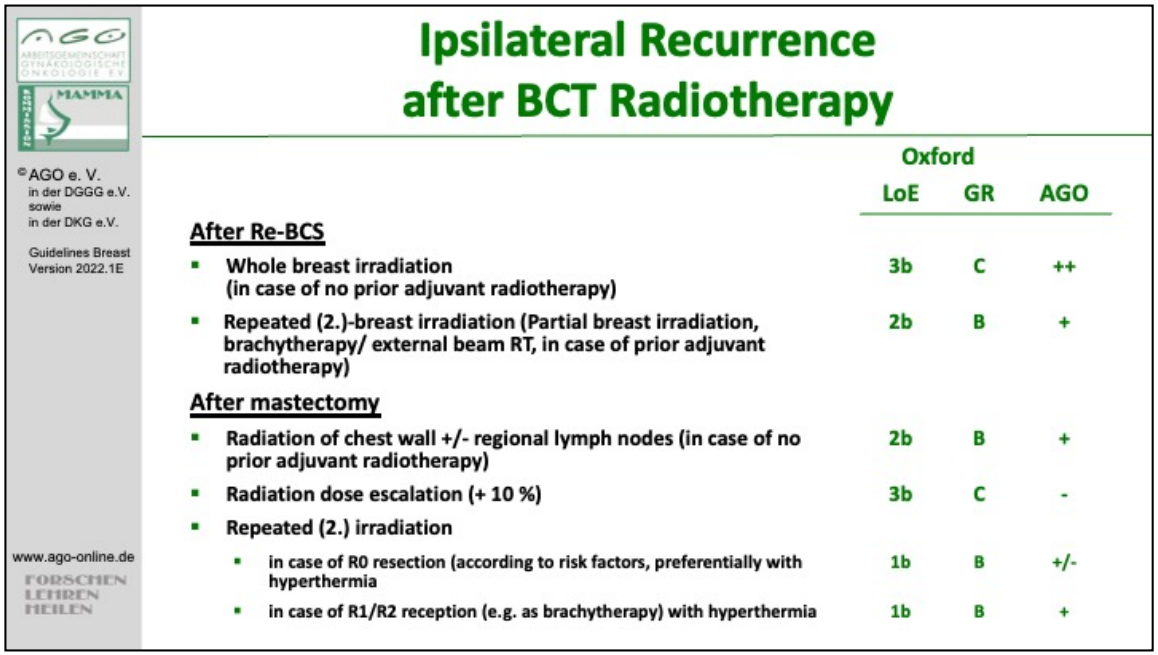
Cochrane Database Syst Rev. 2001;(4)
5. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. NCCN Guidelines (National Comprehensive Cancer Network, 2022); 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.



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
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Statement: Re-irradiation (breast)

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

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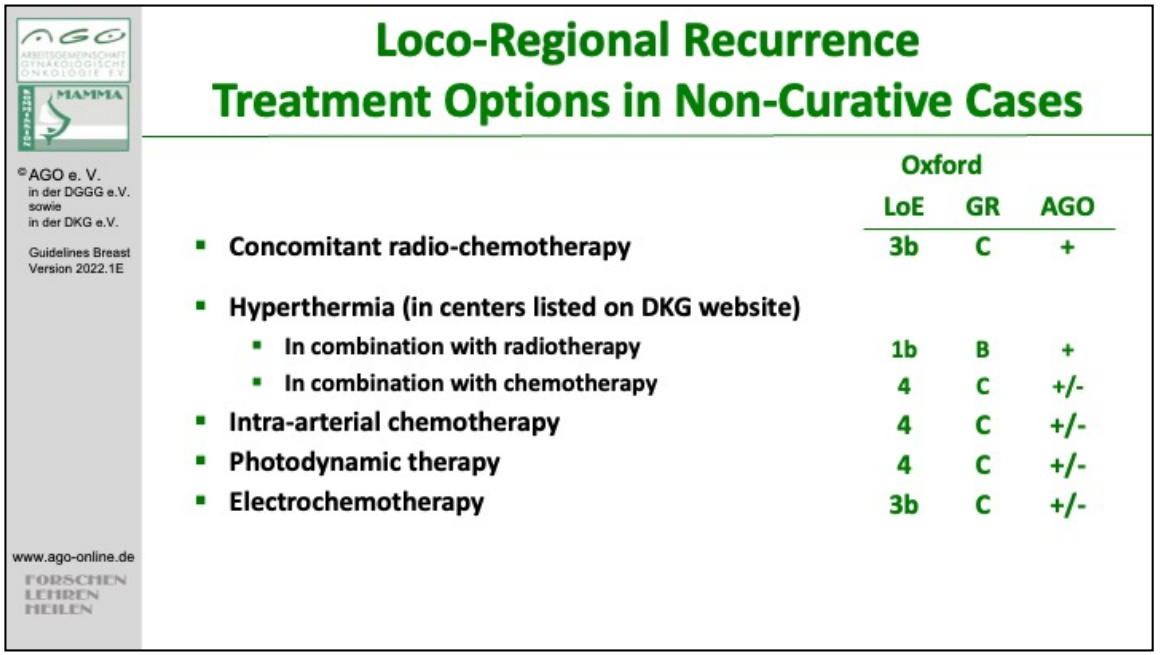

Statement: Concomitant radio-chemotherapy

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Statement: Hyperthermia + radiotherapy +/- chemotherapy

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