Guidelines Breast
Version 2021.1D

FORSCHEN
LEHREN
HEILEN

# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Lokoregionäres Rezidiv


Screened data bases

Pubmed 2005 - 2019, ASCO 2005 – 2020, SABCS 2009 – 2020, 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
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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)

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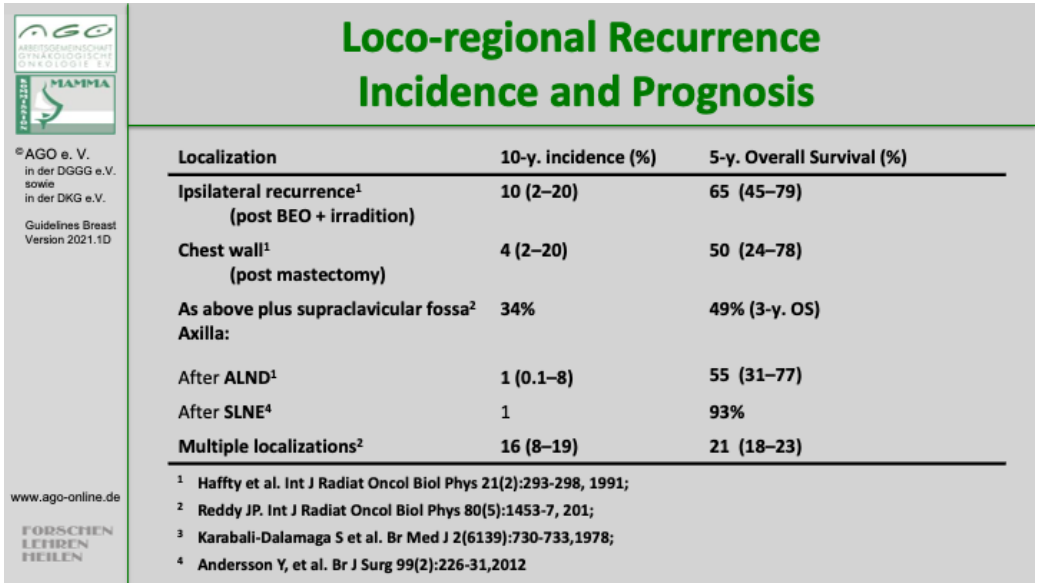



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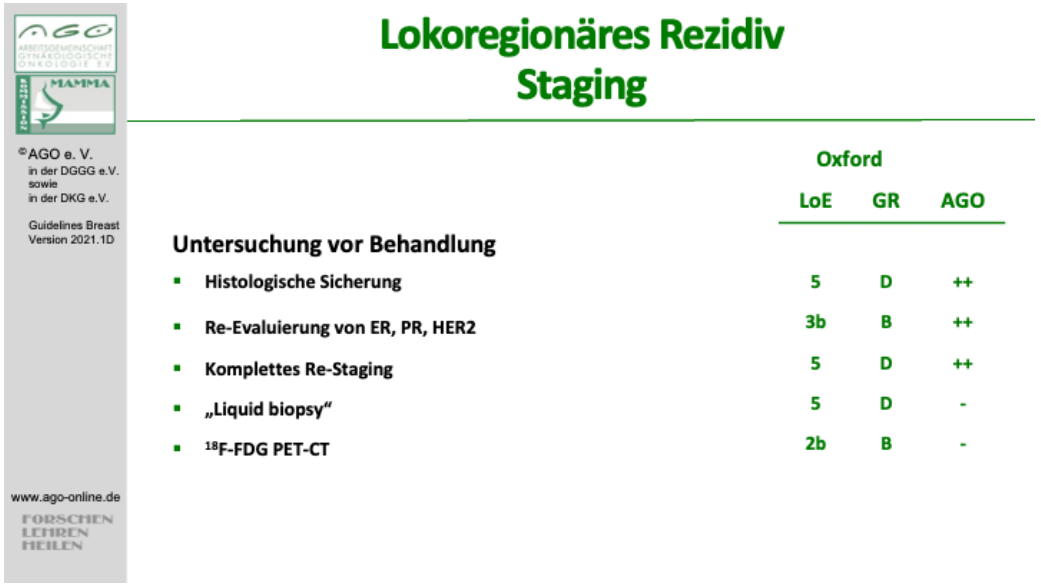



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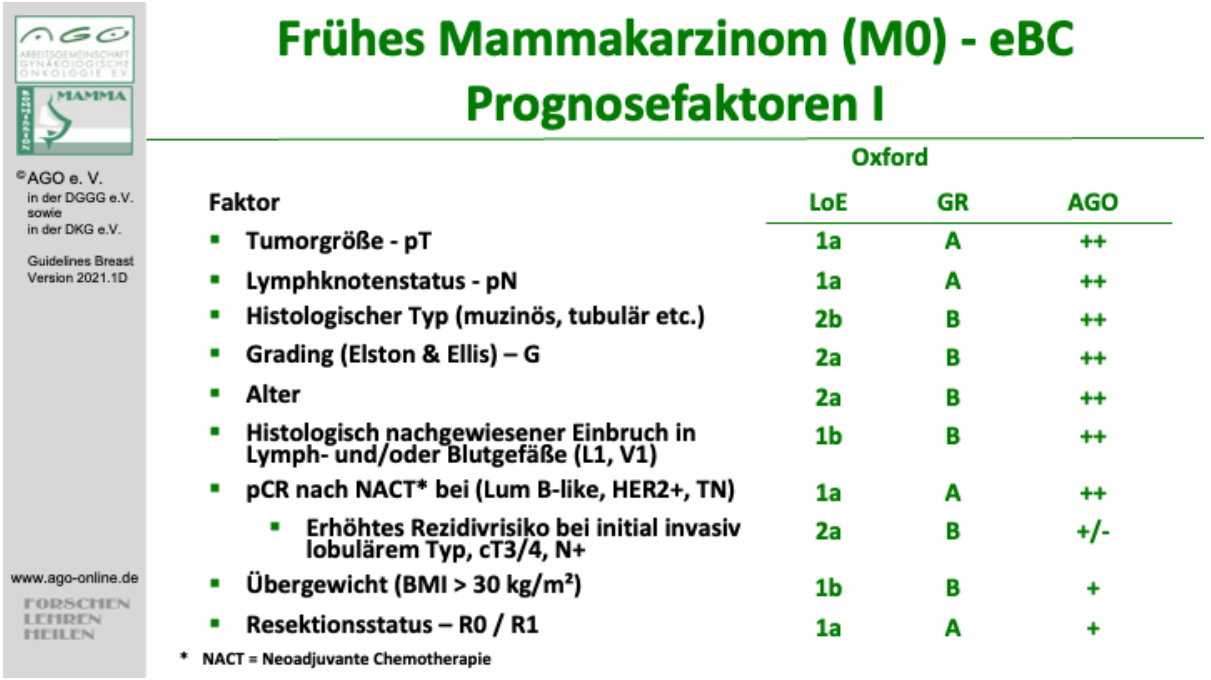



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Tumor size

1. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015 Aug;26(8):1533-46.
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Lymph node status


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Histological type (mucinous, tubular etc.)


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Tumor grade (Elston & Ellis)


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Age


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Histologically proven lymph and/or blood vessel invasion


1. Ryu YJ, Kang SJ, Cho JS et al. Lymphovascular invasion can be better than pathologic complete response to predict prognosis in breast cancer treated with neoadjuvant chemotherapy. Medicine (Baltimore). 2018 Jul;97(30):e11647


pCR after NACT* in Luminal B-like, HER2 and TN Breast Cancer


1. Nekljudova V, Loibl S, von Minckwitz G et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). Contemp Clin Trials. 2018 Aug;71:194-198.
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Increased risk of recurrence in invasive-lobular BC, cT3/4, N+


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1. Chan DSM 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.
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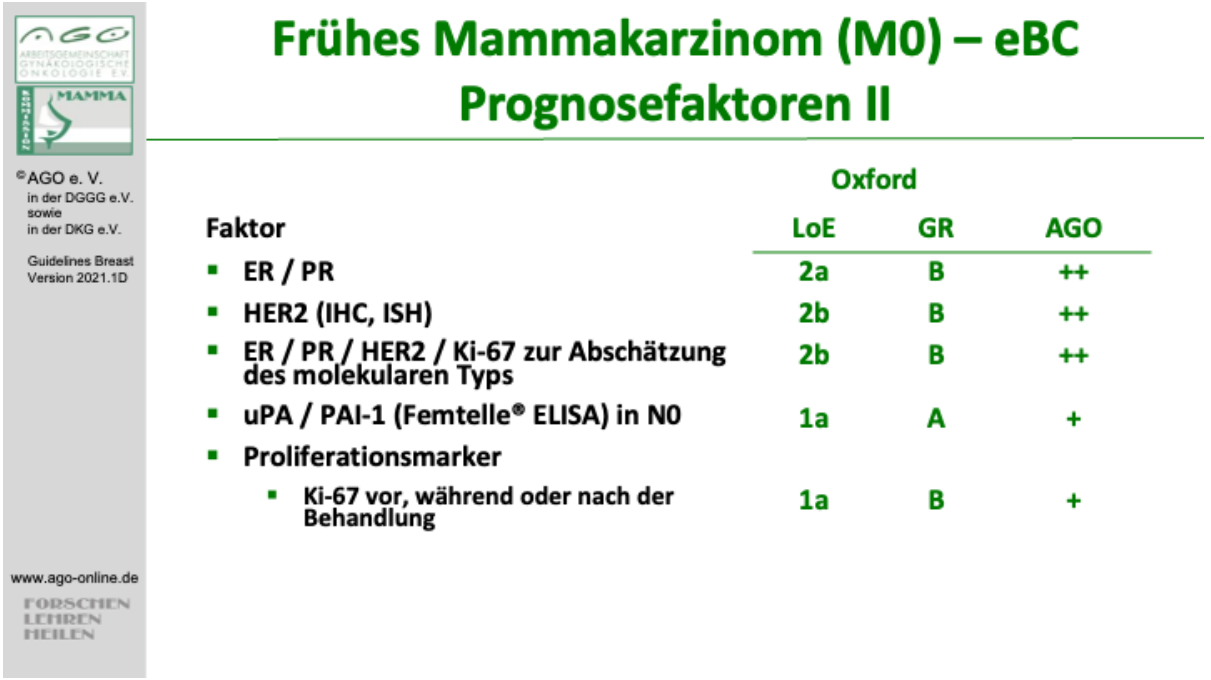



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uPA/PAI-1

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Ki-67

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<u>Post-treatment Ki-67</u>

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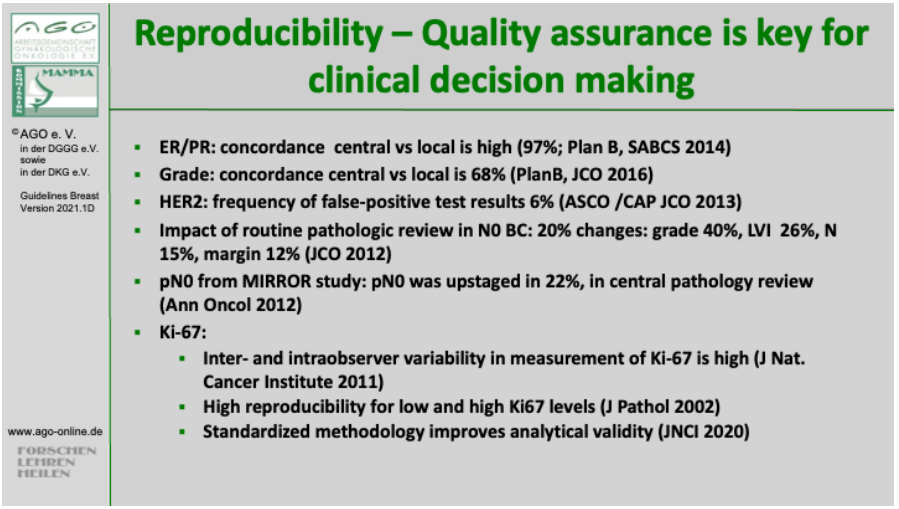



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# Metaanalysis: TNBC and Local Recurrence

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

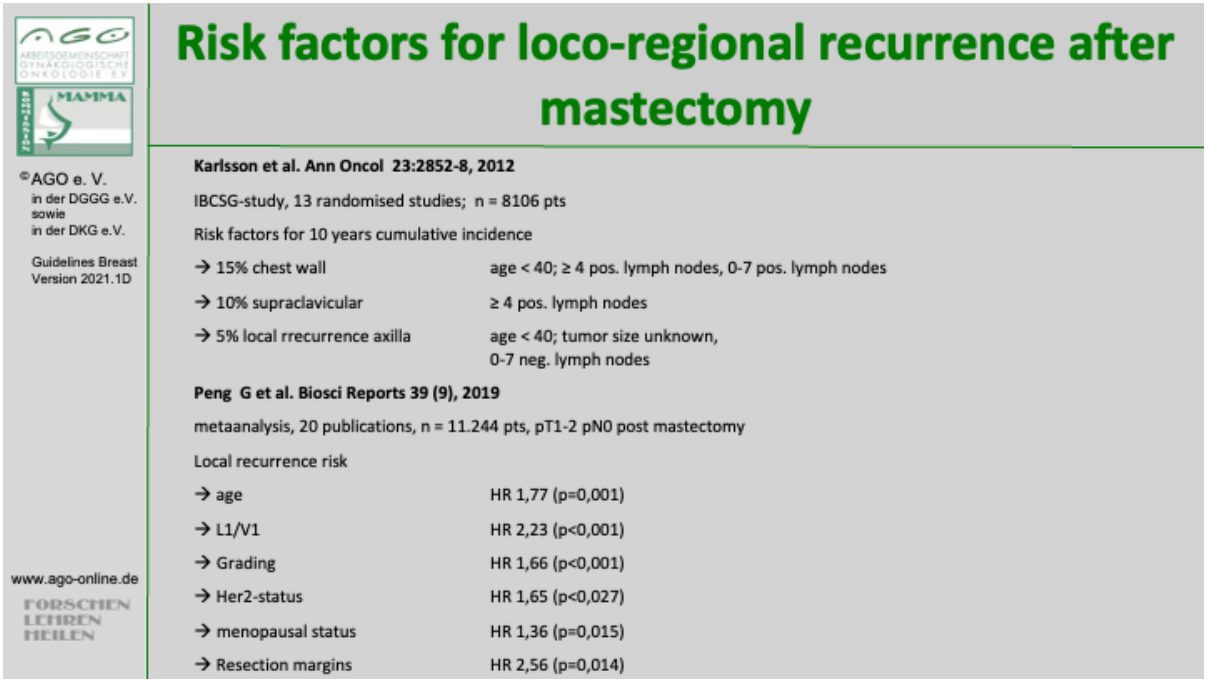
**n = 15312 BC-patients, 22 studies, Hazard-ratios**

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

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

| | | |
|---|---|---|
| **TNBC-subtype** | **vs.** | **HER2-subtype** |
| **ILRR** | **0.69 (0.53–0.91)** | |
| **DM** | **n.s.** | |

**ILRR:** ipsilateral locoregional recurrence
**DM:** distant metastasis
**TNBC:** triple negative breast cancer
**BCT:** breast conserving therapy
**ME:** mastectomy





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

<u>MammaPrint®</u>


1. Slembrouck L, Darrigues L, Laurent C et al. Decentralization of Next-Generation RNA Sequencing-Based MammaPrint® and BluePrint® Kit at University Hospitals Leuven and Curie Institute Paris. Transl Oncol. 2019 Dec;12(12):1557-1565.
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Lobular Score:

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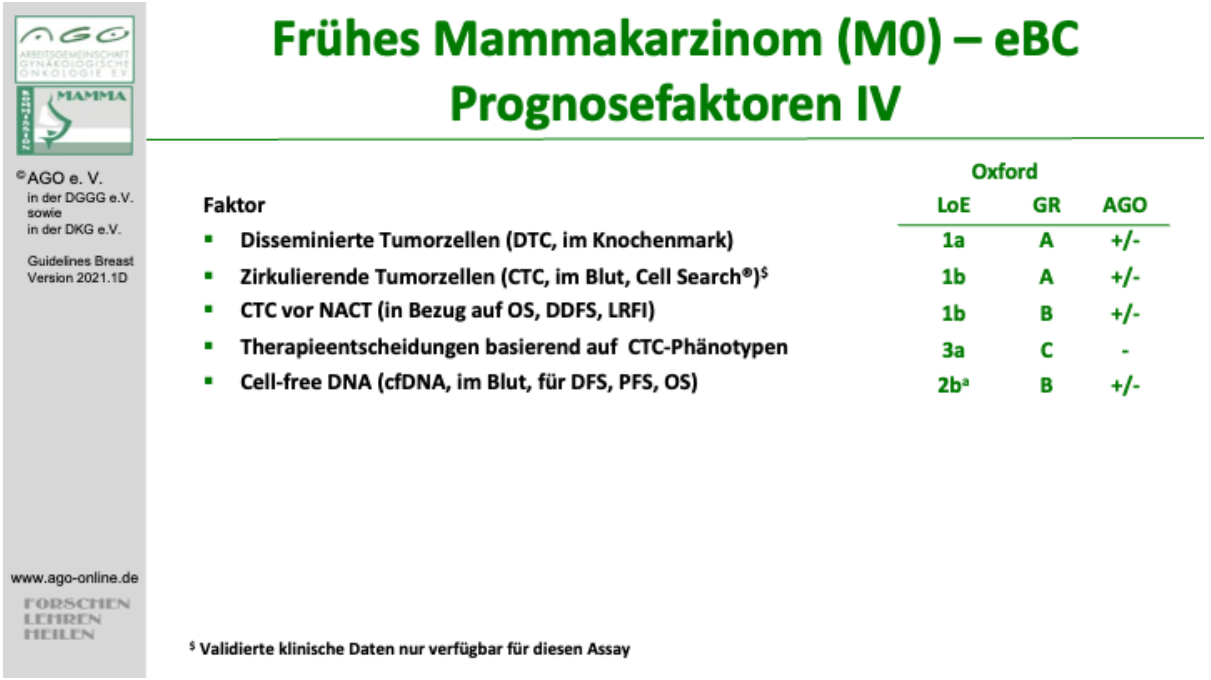


## Frühes Mammakarzinom (M0) – eBC
## Prognosefaktoren IV

| Faktor | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Disseminierte Tumorzellen (DTC, im Knochenmark) | 1a | A | +/- |
| ▪ Zirkulierende Tumorzellen (CTC, im Blut, Cell Search®)$ | 1b | A | +/- |
| ▪ CTC vor NACT (in Bezug auf OS, DDFS, LRFI) | 1b | B | +/- |
| ▪ Therapieentscheidungen basierend auf CTC-Phänotypen | 3a | C | - |
| ▪ Cell-free DNA (cfDNA, im Blut, für DFS, PFS, OS) | 2b[a] | B | +/- |

$ Validierte klinische Daten nur verfügbar für diesen Assay


DTC

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DTC and radiation

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CTC


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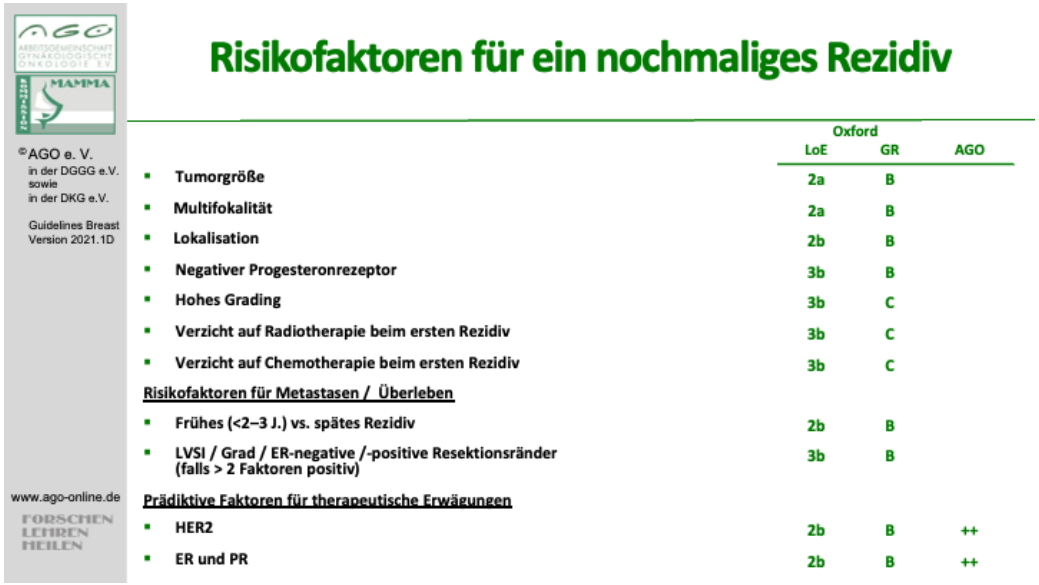


## Risikofaktoren für ein nochmaliges Rezidiv

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| ▪ Tumorgröße | 2a | B | |
| ▪ Multifokalität | 2a | B | |
| ▪ Lokalisation | 2b | B | |
| ▪ Negativer Progesteronrezeptor | 3b | B | |
| ▪ Hohes Grading | 3b | C | |
| ▪ Verzicht auf Radiotherapie beim ersten Rezidiv | 3b | C | |
| ▪ Verzicht auf Chemotherapie beim ersten Rezidiv | 3b | C | |
| **Risikofaktoren für Metastasen / Überleben** | | | |
| ▪ Frühes (<2–3 J.) vs. spätes Rezidiv | 2b | B | |
| ▪ LVSI / Grad / ER-negative /-positive Resektionsränder (falls > 2 Faktoren positiv) | 3b | B | |
| **Prädiktive Faktoren für therapeutische Erwägungen** | | | |
| ▪ HER2 | 2b | B | ++ |
| ▪ ER und PR | 2b | B | ++ |

Parameters in local recurrence to define risk for re-recurrence

Statement: Tumour size

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

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

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

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

Statement: Early vs. Late recurrence

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
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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
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Guidelines Breast
Version 2021.1D



# 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 (+Partialbrustbestrahlung):

1. Sellam Y, Shahadi ID, Gelernter I et al; Local recurrence of breast cancer: Salvage lumpectomy as an option for local treatment. Breast J. 2019 Jul;25(4):619-624.

2. Forster T, Akbaba S, Schmitt D et al; Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation. J Contemp Brachytherapy. 2019;11(4):312-319.
3. Cozzi S, Jamal DN, Slocker A et al; Second breast-conserving therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor recurrence: a retrospective study of 40 patients. J Contemp Brachytherapy. 2019;11(2):101-107.
4. Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database.Hannoun-Levi JM, Gal J, Van Limbergen E, et al. Int J Radiat Oncol Biol Phys. 2020 Dec 29:S0360-3016(20)34722-2. doi: 10.1016/j.ijrobp.2020.12.029.

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

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

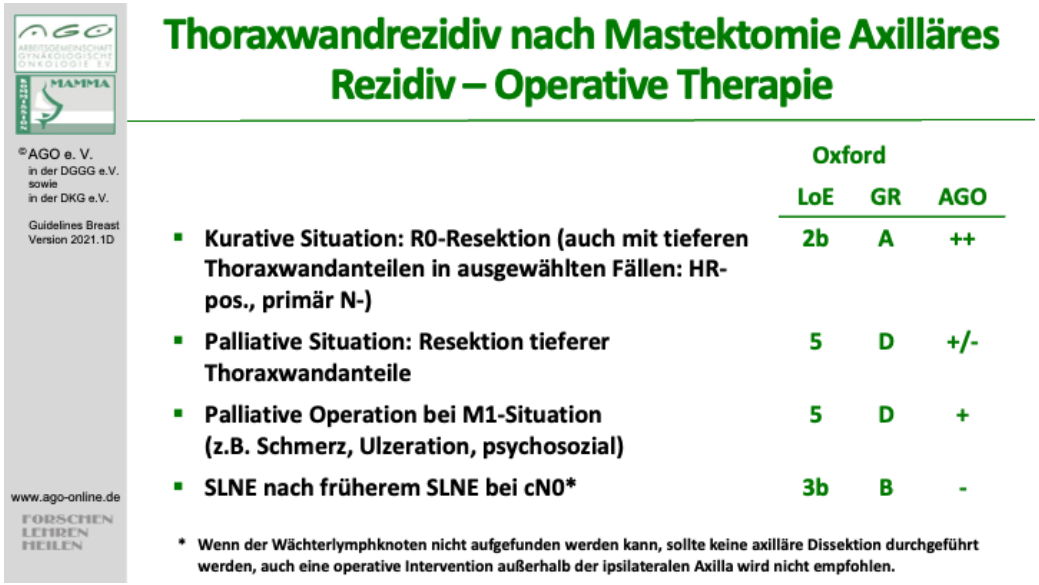
# Mastectomy vs. BCS + partial breast irradiation



Guidelines Breast
Version 2021.1D

- 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




<u>Statement: Curative situation: R0-resection</u>

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

<u>Statement: Palliative situation: Resection of deep parts of the chest wall</u>

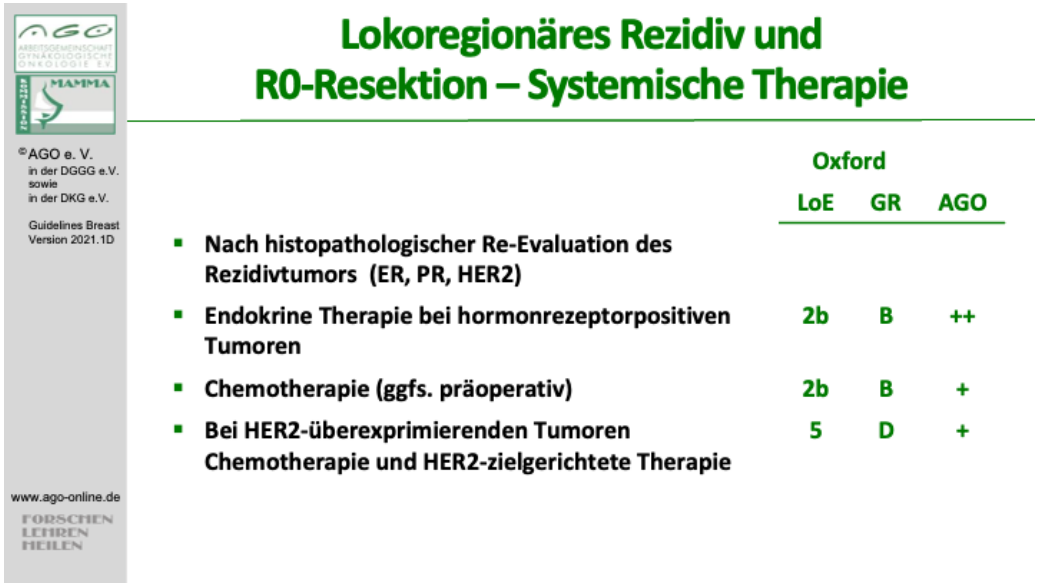
1. Mignano JE, Gage I, Piantadosi S et al; Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treatedwithout postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007
2. Pfannschmidt J, Geisbüsch P, Muley T et al; Surgical resection of secondary chest wall tumors. Thorac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

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

# 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

# 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 – 1.85)** | **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**



Statement: Endocrine therapy in endocrine responsive disease

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

Statement: Chemotherapy (pre- or postoperatively)

1. Kuo SH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiat Oncol Biol Phys 72: 1456-64 (2008)
2. Tokunaga Y, Hosogi H, Nakagami M et al; A case of chest wall recurrence of breast cancer treated with paclitaxel weekly, 5'-deoxy-5-fluorouridine, arterial embolization and chest wall resection. Breast

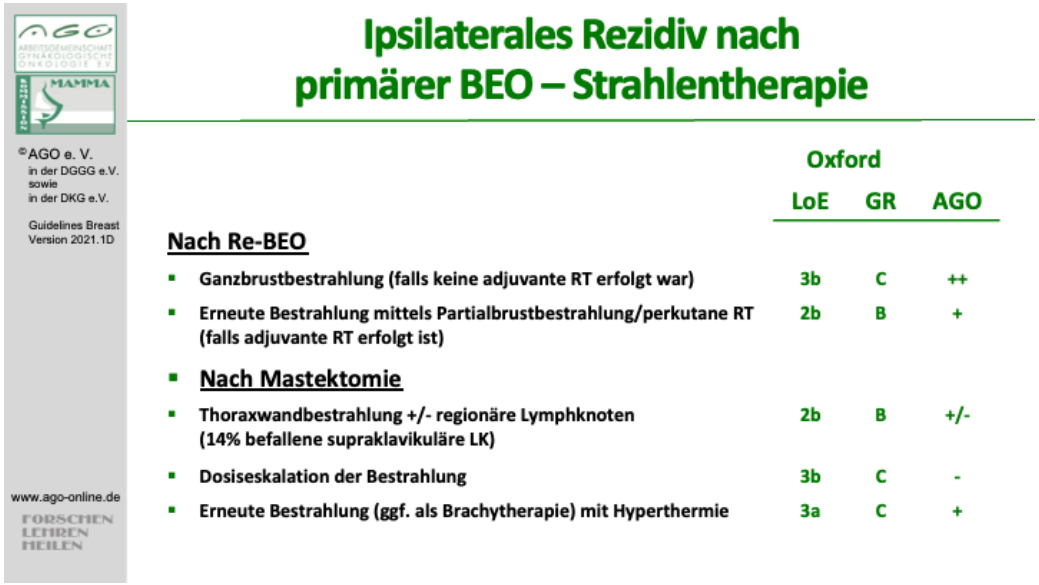
Cancer. 2003;10(4):366-70.
3. Easson AM, McCready DR; Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
4. Rauschecker H, Clarke M, Gatzemeier W et al; Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4)
5. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. NCCN Guidelines (National Comprehensive Cancer Network, 2019); https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf, Version 3.2019 — September 6, 2019 (download 25. Jan. 2020
7. F. Cardoso ,A. Costa , E. Senkus et al; 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259

Statement: Trastuzumab based therapy in HER-2 overexpressing tumors

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

Statement: Checkpoint-Inhibitoren bei PD-L1 Überexpression

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




Statement: Whole breast radiation


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


Statement: Re-irradiation (breast)


1. Hannoun-Levi JM et al; Partial breast irradiation as second conservative treatment for local breast

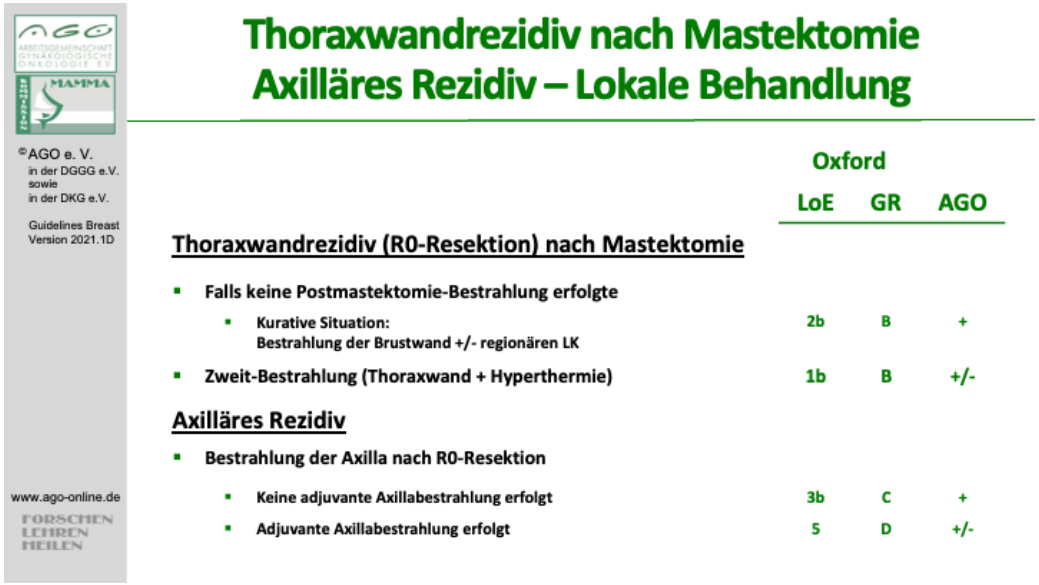
cancer recurrence. Int J Radiat Oncol Biol Phys 60(5):1385-92, 2004
2. Kuerer HM; Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence: the potential role of partial breast irradiation. Cancer 100(11):2269-80, 2004
3. Alpert TE, Kuerer HM, Arthur DW et al; Ipsilateral breast tumor recurrence after breast conservation therapy: outcomesof salvage mastectomy vs. salvage breast-conserving surgery and prognosticfactors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
4. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
5. Skinner HD, Strom EA, Motwani SB et al; Radiation dose escalation for locoregional recurrence of breast cancer after mastectomy. Radiat Oncol 8: 13, 2013
6. Linthorst M, van Geel AN, Baaijens M et al; Re-irradiation and hyperthermia after pulsed dose rate (PDR) brachytherapy moulds for breast cancer local recurrences. Int J Radiat
7. Surgery for recurrent breast cancer . Radiother Oncol 2013;109:188-93
8. Linthorst M, van Geel AN, Baartman EA et al; Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. Strahlenther Onkol 2013;189:387-393
9. Datta NR et al; Hyperthermia and radiation therapy in locoregional recurrent breast cancer: A systematic review and metaanalysis. Int J Rad Oncol 94:1073-87 (2016)
10. Sellam Y, Shahadi ID, Gelernter I et al; Local recurrence of breast cancer: Salvage lumpectomy as an option for local treatment. Breast J. 2019 Jul;25(4):619-624. doi: 10.1111/tbj.13290
11. Forster T, Akbaba S, Schmitt D et al; Second breast conserving therapy after ipsilateral breast tumor recurrence - a 10-year experience of re-irradiation. J Contemp Brachytherapy. 2019 Aug;11(4):312-319. doi: 10.5114/jcb.2019.87001
12. Cozzi S, Jamal DN, Slocker A et al; Second breast-conserving therapy with interstitial brachytherapy (APBI) as a salvage treatment in ipsilateral breast tumor recurrence: a retrospective study of 40 patients. J Contemp Brachytherapy. 2019 Apr;11(2):101-107. doi: 10.5114/jcb.2019.84689
13. Hannoun-Levi JM, Gal J, Van Limbergen E, et al.: Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database. Int J Radiat Oncol Biol Phys. 2020 Dec 29:S0360-3016(20)34722-2. doi: 10.1016/j.ijrobp.2020.12.029.

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
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.
3. 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.
4. Oldenborg S, Valk C, van Os R et al; Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016 Apr;192(4):240-7.

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


<u>Statement: Concomitant radio-chemotherapy</u>


1. Mcormick B; Counterpoint: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):345 – 8, 2007
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
3. Cai G, Cao L, Kirova YM et al; Prospective results of concurrent radiation therapy and weekly paclitaxel as salvage therapy for unresectable locoregionally recurrent breast cancer. Radiat Oncol. 2019;14(1):115.


<u>Statement: Hyperthermia + radiotherapy +/- chemotherapy</u>


1. Mcormick B; Counterpoint: Hyperthermia with radiation therapy for chest wall recurrences. J Natl Compr Canc Netw. 5(3):345 – 8, 2007
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
3. Bischoff J, Lindner LH, Issels RD et al; Clinical impact of locoregional hyperthermia in gynecological oncology. Zentralbl Gynakol 128(5):255-60, 2006

4. Zoul Z; Weekly paclitaxel combined with local hyperthermia in the therapy of breast cancer locally recurrent after mastectomy--a pilot experience. Onkologie. 27(4):385-8, 2004
5. Li G; Local hyperthermia combined with external irradiation for regional recurrent breast carcinoma. Int J Clin Oncol. 9(3):179-83.
6. Oldenborg S, Van Os RM, Van rij CM et al; Elective re-irradiation and hyperthermia following resection of persistent locoregional recurrent breast cancer: A retrospective study. Int J Hyperthermia 26(2):136-44, 2010
7. Vujaskovic Z, Kim DW, Jones E et al; A phase I/II study of neoadjuvant liposomal doxorubicin, paclitaxel, and hyperthermia in locally advanced breast cancer Int J Hyperthermia 26(5):514-21, 2010
8. Kouloulias VE, Koukourakis GV, Petridis AK et al; The efficacy of caelyx and hyperthermia for anticancer treatment. Recent Pat Anticancer Drug Discov 2(3):246-50, 2007
9. Kouloulias VE, Dardoufas CE, Kouvaris JR et al; Liposomal doxorubicin in conjunction with reirradiation and local hyperthermia treatment in recurrent breast cancer: a phase I/II trial. Clin Cancer Res 8(2):374-82,2002
10. Feyerabend T, Wiedemann GJ, Jäger B et al; Local hyperthermia, radiation, and chemotherapy in recurrent breast cancer is feasible and effective except for inflammatory disease. Int J Radiat Oncol Biol Phys Apr 1;49(5):1317-25, 2001
11. Linthorst M, Baaijens M, Wiggenraad R et al; Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Radiother Oncol 2015; May 19
12. De-Colle C, Weidner N, Heinrich V et al; Hyperthermic chest wall re-irradiation in recurrent breast cancer: a prospective observational study. Strahlenther Onkol. 2019;195(4):318-326.
13. Dharmaiah S1, Zeng J2, Rao VS et al; Clinical and dosimetric evaluation of recurrent breast cancer patients treated with hyperthermia and radiation. Int J Hyperthermia. 2019;36(1):986-992.

Statement: Intraarterial chemotherapy

1. Murakami M, Kuroda Y, Nishimura S et al; Intraarterial infusion chemotherapy and radiotherapy with or without surgery for patients with locally advanced or recurrent breast cancer. Am J Clin Oncol 24(2):185-91, 2001

Statement: Photodynamic therapy

1. Allison R, Mang T, Hewson G et al; Photodynamic therapy for chest wall progression from breast carcinoma is an underutilized treatment modality. Cancer 91(1):1-8,2001.
2. Wyss P, Schwarz V, Dobler-Girdziunaite D et al;Photodynamic therapy of locoregional breast cancer recurrences using a

chlorin-type photosensitizer Int J Cancer. 93(5):720-4, 2001

Statement: Electrochemotherapy

1. Campana LG, Valpione S, Falci C et al; The activity and safety of electrochemotherapy in persistent chest wall recurrence from breastcancer after mastectomy: a phase-II study. Breast Cancer Res Treat 134(3):1169-78, 2012
2. Matthiessen LW, Johannesen HH, Hendel HW et al; Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 51(6):713-212012
3. Sersa G, Cufer T, Paulin SM et al; Cancer Treat Rev. Electrochemotherapy of chest wall breast cancer recurrence 38(5):379-86, 2012