

Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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Guidelines Breast
Version 2017.1

Loco-Regional Recurrence

Loco-regional Recurrence

➤ Version 2002:

Brunnert / Simon

➤ Versions 2003–2016:

**Audretsch / Bauerfeind / Budach / Costa
/ Dall / Fehm / Fersis / Friedrich / Gerber /
Göhring / Hanf / Harbeck / Lisboa /
Maass / Mundhenke / Rezai / Solomayer /
Souchon / Thomssen / Wenz**

➤ Version 2017:

Bauerfeind / Thomssen

Loco-regional Recurrence Incidence and Prognosis

Localization	Frequency (%)	5-y. Overall Survival (%)
Ipsilateral recurrence¹ (post BCT + irradiation)	10 (2–20)	65 (45–79)
Chest wall¹ (post mastectomy)	4 (2–20)	50 (24–78)
As above plus supraclavicular fossa²	34%	49% (3-y. OS)
Axilla:		
After ALND¹	1 (0.1–8)	55 (31–77)
After SNB⁴	1	93%
Multiple localizations²	16 (8–19)	21 (18–23)

¹ Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991; ²Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 2011; ³Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978; ⁴Andersson Y, et al. Br J Surg 99(2):226-31,2012

Loco-regional Recurrence Staging

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Examinations before treatment:

➤ Tissue biopsy	5	D	++
➤ Re-assessment of ER, PgR, HER2	3b	B	++
➤ Complete re-staging	5	D	++

Risk Factors for Loco-Regional Recurrence at Primary Diagnosis

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Increased risk for loco-regional recurrence

- | | |
|--|-----|
| ➤ Young age | 1a |
| ➤ Positive microscopic margins (R1) of the primary tumor | 1a |
| ➤ Omitting adjuvant radiotherapy (if indicated) | 1a |
| ➤ Extensive intraductal component | 1b |
| ➤ Vessel invasion | 1b |
| ➤ HER2 positive and triple negative > Luminal B-like
> luminal A-like | 2a |
| ➤ Number of involved lymph nodes | 1a |
| ➤ Grading (G3) | 1b* |
| ➤ Elevated proliferation markers: e.g. Ki67; | 2b |
| ➤ pT (> 2) | 1b* |
| * node negative | 1a |
| ➤ Inflammatory breast cancer | 2b |
| ➤ Medial tumor localisation | 4 |
| ➤ Obesity (Body mass index) | 1a |

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

Risk Factors for Locoregional Recurrences after ME



Karlsson et al. Ann Oncol 23:2852-8, 2012

IBCSG-study, 13 randomized trials, n= 8106 patients

Risk factors for 10 yr. cumulative incidence ...:

...> **15% chest wall:** age <40; ≥ 4 pos. nodes, 0-7 uninvolved nodes

...> **10% supraclavicular:** ≥ 4 pos. nodes

...> **5% axillary failure:** age < 40; unknown tumor size, 0-7 uninvolved nodes

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Metaanalysis: 7174 BCT and 5418 ME

Lowery AJ et al. Breast Cancer Res Treat 133(3):831-41, 2012

After BCT:

HR-positive tumors show a lower risk for LRR than...
triple negative tumors (RR 0.38) and....
HER2-expressing tumors (RR 0.34)*

After ME:

HR-positive tumors show a lower risk for LRR than...
HER2-expressing tumors (RR 0.69)* and...
triple negative tumors (RR 0.61)

Result:

HR-positive tumors exhibit the lowest rate of local recurrence.

***most pts. were treated in the time before routine adjuvant trastuzumab use**

Loco-regional Recurrence Prognostic / Predictive factors

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Parameters of the locally recurrent tumor to define the risk for re-recurrence

- | | | |
|----------------------------------|----|---|
| ➤ Tumor size | 2a | B |
| ➤ Multifocality | 2a | B |
| ➤ Localisation | 2b | B |
| ➤ Negative progesterone receptor | 3b | B |

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 PgR | 2b | B | ++ |

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 pat., retrospective cohort-study
pT1/2, N0 tumors, breast conserving treatment
269 ipsilateral breast tumor recurrences (IBTR)

Multivariate analysis:

TTR <48 months

LVSI (of the LRR)

ER negative LR-tumor

high grade

close margins of recurrent tumor

=> if ≥ 2 factors positive => worse OS



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Ipsilateral Recurrence after BCT Surgery

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- **Mastectomy (aim: R0)**
- **Re-BCS with tumor-free margins (R0)**
- **Axillary intervention after prior AxDissection if cN0**
- **SLNE after prior SLNE if cN0***
- **Palliative surgery in M1-situation
(e.g. pain, ulceration, psychosocial indication)**

3b	B	++
3b	C	+/-
4	C	-
1b	B	-
5	D	+

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***If no sentinel lymph node can be identified, axillary dissection is not recommended; no operation outside the ipsilateral axilla is recommended**

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery

	Oxford LoE / GR	AGO	
➤ Curative situation: R0-resection	2b	A	++
➤ Palliative situation: Resection of deep parts of the chest wall	5	D	+/-
➤ Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)	5	D	+

Loco-regional Recurrence after R0-Resection

Systemic Treatment

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According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

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- | | | | |
|--|----|---|----|
| ➤ Endocrine therapy in endocrine responsive tumors | 2b | B | ++ |
| ➤ Chemotherapy (consider preoperative) | 2b | B | + |
| ➤ In case of HER2 positive disease, chemotherapy + HER2 targeted therapy | 5 | D | + |

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Chemo Therapy by Loco-regional Recurrence

➤ CALOR Trial

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).

Locoregional Recurrence in Case R0 Resection not Likely - Systemic Treatment

According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)

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LoE / GR

- | | | | |
|---|----|---|----|
| ➤ Endocrine therapy in endocrine responsive tumors | 2b | B | ++ |
| ➤ Chemotherapy (pre- or postoperatively) | 2b | B | ++ |
| ➤ HER2-targeted therapy in HER2-positive tumors (with chemotherapy) | 5 | D | ++ |

Ipsilateral Recurrence after BCT Radiotherapy

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After Re-BCS

- Whole breast irradiation
(in case adjuvant radiotherapy was not performed)
- Re-breast irradiation (Partial breast radiation,
brachytherapy, external beam RT)

3b C ++

3b C +/-

After mastectomy

- Radiation of chest wall +/- regional lymph nodes
(14% involved supraclavicular metastases)
- Radiation dose escalation (+10%)
- Repeated irradiation (e.g. as brachytherapy)
with hyperthermia

2b B +/-

3b C -

3a C +/-

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Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy

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Chest-Wall Recurrence after Mastectomy

- If no prior postmastectomy radiotherapy
 - Curative situation: irradiation of the chest wall +/- regional lymph nodes
- Re-irradiation (chest wall + hyperthermia)

2b	B	+
1b	B	+/-

Axillary recurrence

Irradiation of axilla after R0-surgery

- No prior adjuvant irradiation of the axilla
- Adjuvant irradiation of the axilla

3b	C	+
5	D	+/-

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Loco-Regional Recurrence Treatment Options in Non Curative Cases

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➤ 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	+/-

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Loco-regional Recurrence (2/18)

Further information and references:

Screened data bases: Pubmed 2005 - 2017, ASCO 2005 – 2017, SABCS 2009 – 2017, Cochrane data base

Guidelines:

1. F. Cardoso ,A. Costa , E. Senkus , M. Aapro, F. Andre, C.H. Barrios , J. Bergh, G. Bhattacharyya , L. Biganzoli , M.J. Cardoso , L. Carey , D. Corneliussen-James , G. Curigliano , V. Dieras , N. El Saghir , A. Eniu , L. Fallowfield , D. Fenech , P. Francis , K. Gelmon , A. Gennari, N. Harbeck , C. Hudis , B. Kaufman, I. Krop , M. Mayer , H. Meijer , S. Mertz , S. Ohno , O. Pagani , E. Papadopoulos , F. Peccatori , F. Penault-Llorca , M.J. Piccart , J.Y. Pierga , H. Rugo , L. Shockney , G. Sledge , S. Swain , C. Thomssen , A. Tutt , D. Vorobiof , B. Xu , L. Norton , E. Winer. 3rd ESOeESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) The Breast 31 (2017) 244e259
2. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordström EB, Pagani O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B, Winer E. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014 Oct;23(5):489-502.
3. Lin NU, Thomssen C, Cardoso F, Cameron D, Cufer T, Fallowfield L, Francis PA, Kyriakides S, Pagani O, Senkus E, Costa A, Winer EP: European School of Oncology-Metastatic Breast Cancer Task Force. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013 Jun;22(3):203-10.
4. NCCN (National Comprehensive Cancer Network, 2012); http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (download 13. Jan. 2013)

5. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL;
http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf
6. Harms W, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Krug D, Piroth MD, Sautter-Bihl ML, Sedlmayer F, Souchon R, Wenz F, Sauer R; 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.

Loco-regional Recurrence Incidence and Prognosis (3/18)

Further information:

About 10 (2-20 %) of patients who undergo breast-conservation surgery and radiation therapy will subsequently develop ipsilateral breast tumor recurrence. Chest wall recurrences after mastectomy and isolated axillary recurrences are relatively rare events. Although the local outcome following salvage therapy is quite good, the risk of distant metastases for patients with local recurrence is three to five times greater than for those without recurrence. The reason for this association has been controversially discussed, but it now appears that local recurrence is both a marker of the underlying biological aggressiveness of the tumor and a possible source for further tumor dissemination. The slide denotes 5 year overall survival rates of 65 %, 50 %, 55 % and 21 % after recurrences in ipsilateral breast, chest wall, axilla or multiple localisations, respectively. The patients with loco-regional recurrence survived almost significantly better than those with distant recurrence. The disease-free time-to-recurrence correlated positively with the time of survival after a recurrence. Isolated recurrences in the ipsilateral supraclavicular fossa fare as well as isolated chest wall recurrences, whereas locoregional recurrences of any site fare worse if the supraclavicular fossa is additionally affected: the 3-year overall survival has been determined with only 49%. Axillary recurrence after sentinel lymph node biopsy is a rare event and occurs in approx. 1% of patients with initially negative sentinel lymph node biopsy. The survival rate is higher than 90 % in these patients.

References:

1. Haffty BG, Fischer D, Beinfield M, McKhann C. Prognosis following local recurrence in the conservatively treated breast cancer patient. *Int J Radiat Oncol Biol Phys* 21(2):293-298, 1991
2. Reddy JP, Levy L, Oh JL, Strom EA, Perkins GH, Buchholz TA, Woodward WA. Long-term outcomes in patients with isolated supraclavicular nodal recurrence after mastectomy and doxorubicin-based chemotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 80(5):1453-7, 2011
- Karabali-Dalamaga S., Souhami R. L., O'Higgins N. J., Soumilas A., Clark C. G. Natural history and prognosis of recurrent breast cancer. *Br Med J* 2(6139):730-733, 1978

3. Andersson Y, de Boniface J, Jönsson PE, Ingvar C, Liljegren G, Bergkvist L, Frisell J; 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
4. Lowery AJ¹, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ.:Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype.*Breast Cancer Res Treat.* 2012 Jun;133(3):831-41. doi: 10.1007/s10549-011-1891-6. Epub 2011 Dec 7.
5. www.tumorregister-muenchen.de

Loco-regional Recurrence Staging (4/18)

Further information:

The 5-year overall survival of patients with isolated loco-regional recurrence amounted to 50%. There are no data about the frequency of distant metastases detected by modern staging examinations at time of recurrence. Moreover there are no studies confirming an implication of the re-staging findings in systemic treatment or improvement of overall survival of asymptomatic patients with resectable loco-regional recurrence. Nevertheless to avoid „over- or undertreatment“ and to prevent complications the AGO recommends a re-staging in all patients with resectable recurrences. Re-staging can be performed by conventional techniques, CT scans, MRI or Pet scans depending of practioners choice.

References:

1. Veronesi U, Marubini E, Del Vecchio M, Manzari A, Andreola S, Greco M, Luini A, Merson M, Saccozzi R, Rilke F. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. J Natl Cancer Inst 87(1):19-27, 1995
2. Hölzel D, Engel L, Schmidt M, Sauer H. 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, Lee A, Cornford E, James J, Ellis I. 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 , M. Aapro, F. Andre, C.H. Barrios , J. Bergh, G. Bhattacharyya , L. Biganzoli , M.J. Cardoso , L. Carey , D. Corneliussen-James , G. Curigliano , V. Dieras , N. El Saghir , A. Eniu , L. Fallowfield , D. Fenech , P. Francis , K. Gelmon , A. Gennari, N. Harbeck , C. Hudis , B. Kaufman, I. Krop , M. Mayer , H. Meijer , S. Mertz , S. Ohno , O. Pagani , E. Papadopoulos , F. Peccatori ,F. Penault-Llorca , M.J. Piccart , J.Y. Pierga , H. Rugo , L. Shockney , G. Sledge , S. Swain , C. Thomssen , A. Tutt , D. Vorobiof , B. Xu , L. Norton , E. Winer. 3rd ESOeESMO international consensus guidelines for Advanced SBreast Cancer (ABC 3) The Breast 31 (2017) 244e259

Loco-regional Recurrence Risk Factors at Primary Diagnosis (5/18)

Further information:

Risk factors for IBTR include tumor size, nodal status, estrogen receptor status, molecular subtype, young age, positive microscopic margins, extensive intraductal component, higher grading, vessel invasion multifocality, an extensive intraductal component, and lymphatic vessel invasion. Multivariate analysis stratified by treatment showed that age was an independent prognostic factor for local control. Systemic treatment and radiation therapy significantly reduced local recurrence.

References:

Informative for the whole list of factors:

1. Sestak I, Dowsett M, Ferree S, Baehner FL, Cuzick J. 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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fischer ER, Jeong JH, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 347: 1233–124, 2002
 5. Truong PT 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
 6. Smith TE, Lee D, Turner BC, Carter D, Haffty BG. 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
 7. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after Breast Cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat* 133(3):831-41, 2012
 8. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N: 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
 9. Hunt KK, Ballman KV, McCall LM, Boughey JC, Mittendorf EA, Cox CE, Whitworth PW, Beitsch PD, Leitch AM, Buchholz TA, Morrow MA, Giuliano AE. Factors associated with local-regional recurrence after a negative sentinel node dissection: results of the ACOSOG Z0010 trial. *Ann Surg* 256(3):428-36, 2012
 10. 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
 11. Kindts I, Buelens P, Laenen A, Van Limbergen E, Janssen H, Wildiers H, Weltens C. Omitting radiation therapy in women with triple-negative breast cancer leads to worse breast cancer-specific survival. *Breast.* 2016 Dec 21;32:18-25.

Statement: Young age

1. van der Hage JA, Mieog JS, van de Velde CJ, Putter H, Bartelink H, van de Vijver MJ. 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, Lacruz Bassols M, ReigCastillejo A, Quera Jordana J, Membrive Conejo I, Lozano Galán J, Rodríguez deDios N: 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, Bonnema J, Bartelink H, van de Velde CJ. 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
4. Jobsen JJ, van der Palen J, Merrwaldt JH. The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy. *Eur J Cancer* 37: 1820–1827, 2001
5. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JC, Jager JJ, Bing Oei S, Peterse HL, Pierart M, Poortmans PM, Struikmans H, Van den Bogaert W, Bartelink H EORTC Radiotherapy, Breast Cancer Groups. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer* 39(7): 932–944, 2003
6. Elder EE, Kennedy CW, Gluch L, Carmalt HL, Janu NC, Joseph MG, Donellan MJ, Molland JG, Gillett DJ: Patterns of breast cancer relapse. *Eur J Surg Oncol.* 32(9):922-7, 2006
7. Oh JL, Bonnen M, Outlaw ED, Schechter NR, Perkins GH, Strom EA, Babiera G, Oswald MJ, Allen PK, Thames HD, Buchholz TA. The impact of young age on locoregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: How young is "young"? *Int J Radiat Oncol Biol Phys* 65(5):1345-52, 2006
8. 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* 23: 2852-8, 2012
9. Cronin PA, Olcese C, Patil S, Morrow M, Van Zee KJ Impact of Age on Risk of Recurrence of Ductal Carcinoma In Situ: Outcomes of 2996 Women Treated with Breast-Conserving Surgery Over 30 Years. *Ann Surg Oncol.* 2016 Sep;23(9):2816-24.

Statement: Positive microscopic margins

1. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ: 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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
4. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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
5. Pilewskie M, Ho A, Orell E, Stempel M, Chen Y, Eaton A, Patil S, Morrow M Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast-conserving therapy.. *Ann Surg Oncol*. 2014 Apr;21(4):1209-14.
6. Bosma SC, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, Rutgers EJ, van de Vijver MJ, Elkhuizen PH. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. *Breast Cancer Res Treat*. 2016 Apr;156(2)
7. Dixon JM, Thomas J, Kerr GR, Williams LJ, Dodds C, Kunkler IH, Macaskill EJ. A study of margin width and local recurrence in breast conserving therapy for invasive breast cancer. *Eur J Surg Oncol*. 2016 May;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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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* 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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
3. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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. Truong PT, Yong CM, Abnoui F, Lee J, Kader HA, Hayashi A, Olivotto IA: 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

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, Putter H, Bartelink H, van de Vijver MJ 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. Canello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, Montagna E, Dellapasqua S, Iorfida M, Cardillo A, Veronesi P, Luini A, Intra M, Gentilini O, Scarano E, Goldhirsch A, Colleoni M. Prognosis in women with small node-negative operable breast cancer by immunohistochemically selected subtypes, *Breast Cancer Res Treat* 127:713-20, 2011
3. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997

4. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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
5. 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
6. Dominici LS, Mittendorf EA, Wang X, Liu J, Kuerer HM, Hunt KK, Brewster A, Babiera GV, Buchholz TA, Meric-Bernstam F, Bedrosian I. Implications of constructed biologic subtype and its relationship to locoregional recurrence following mastectomy. *Breast Cancer Res* 23;14(3):R82, 2012
7. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after Breast Cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat* 133(3):831-41, 2012
8. 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
9. *World J Surg Oncol.* 2014; 12: 289. Published online 2014 Sep 20. doi: 10.1186/1477-7819-12-289 PMCID: PMC4190445 HER-2 positive breast cancer is associated with an increased risk of positive cavity margins after initial lumpectomy Haixia Jia, Weijuan Jia, Yaping Yang, Shunrong Li, Huiyi Feng, Jieqiong Liu, Nanyan Rao, Liang Jin, Jiannan Wu, Ru Gu, Liling Zhu, Kai Chen, Heran Deng, Yunjie Zeng, Qiang Liu, Erwei Song, and Fengxi Su *Asian Pac J Cancer Prev.* 2014;15(1):315-20
10. Lai SF, Chen YH, Kuo WH, Lien HC, Wang MY, Lu YS, Lo C, Kuo SH, Cheng AL, Huang CS. 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.
11. Braunstein LZ, Taghian AG, Niemierko A, Salama L, Capuco A, Bellon JR, Wong JS, Punglia RS, MacDonald SM, Harris JR. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. *Breast Cancer Res Treat.* 2017 Jan;161(1):173-179.
12. Jwa E, Shin KH, Kim JY, Park YH, Jung SY, Lee ES, Park IH, Lee KS, Ro J, Kim YJ, Kim TH. 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.

Statement: Grading G3

1. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ: 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, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. 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
3. *Am J Clin Oncol*. 2014 Oct;37(5):486-91. doi: 10.1097/COC.0b013e31827e54c2.
Risk factors for locoregional recurrence after mastectomy in stage T1 N0 breast cancer.

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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
4. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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
5. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. 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. 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
7. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
8. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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
9. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. 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
10. Buchanan CL, Dorn PL, Fey J, Giron G, Naik A, Mendez J, Murphy C, Sclafani LM. Locoregional recurrence after mastectomy: incidence and outcomes. *J Am Coll Surg.* 203: 469-74, 2006
11. Livi L, Paiar F, Simontacchi G, Barca R, Detti B, Fondelli S, Bastiani P, Santini R, Scotti V, Bianchi S, Cataliotti L, Mungai V, Biti G. 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
12. Breast Cancer. 2014 May;21(3):292-301. doi: 10.1007/s12282-012-0391-9. Epub 2012 Aug 14. Locoregional recurrence risk factors and the impact of postmastectomy radiotherapy on patients with tumors 5 cm or larger. Nagao T1, Kinoshita T, Tamura N, Hojo T, Morota M, Kagami Y. Author information 1 Department of Breast Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

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

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. Dalberg K, Mattsson A, Rutqvist LE, Johansson U, Riddez L, Sandelin K. Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
4. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, Dindtner J, Thurlimann B, Fey M, Werner ID, Forbes JF, Price K, Coates AS, Collins J. 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
5. Jagsi R, Raad RA, Goldberg S, Sullivan T, Michaelson J, Powell SN, Taghian AG. 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
6. Cheng SH, Horng CF, Clarke JL, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. 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
7. Truong PT, Jones SO, Kader HA, Wai ES, Speers CH, Alexander AS, Olivotto IA. 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
8. *Curr Oncol.* 2014 Oct;21(5):e685-90. doi: 10.3747/co.21.2000 Risk factors for locoregional recurrence after postmastectomy radiotherapy in breast cancer patients with four or more positive axillary lymph nodes. Li Q1, Wu S2, Zhou J3, Sun J1, Li F1, Lin Q2, Guan X1, Lin H1, He Z1
9. 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, Reimer T, Fietkau R. 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, Gelmon K, Nielsen TO, Kennecke H. 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: Nomograms

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. After neoadjuvant chemotherapy: 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

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, Chen X, Rui R, Liu C, Sun Y, Liu L, Gong J, Yuan P. 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, Saeed H, Prior P, Rein L, Szabo A, Wilson JF, Currey A, DWhite J 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, Truong L, Catalano PJ, Bellon JR. Body Mass Index and Locoregional Recurrence in Women with Early-Stage Breast Cancer. *Ann Surg Oncol.* 2016 Nov;23(12):3870-3879.

Recent evidence for Multigene arrays predicting risk for local relapse:

1. Drukker CA¹, Elias SG, Nijenhuis MV, Wesseling J, Bartelink H, Elkhuizen P, Fowble B, Whitworth PW, Patel RR, de Snoo FA, van 't Veer LJ, Beitsch PD, Rutgers EJ. 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. Erratum to: Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Drukker CA, Elias SG, Nijenhuis MV, Wesseling J, Bartelink H, Elkhuizen P, Fowble B, Whitworth PW, Patel RR, de Snoo FA, Van't Veer LJ, Beitsch PD, Rutgers EJ. *Breast Cancer Res Treat.* 2015 Jan 21.
3. Fitzal F, Filipits M, Fesl C, Rudas M, Dubsy PC, Bartsch R, Regitnig P, Bauernhofer T, Greil R, Leitner G, Knauer M, Hubalek M, Fridrik MA, Herz W, Dietze O, Cowens JW, Ferree S, Nielsen TO, Gnant M. Predicting local recurrence using PAM50 in postmenopausal endocrine responsive breast cancer patients. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 1008)

Metaanalysis: TNBC and Local Recurrence (6/18)

No further information

No references

Risk Factors for Locoregional Recurrence after ME (7/18)

No further information

No references

Metaanalysis: 7174 BCT and 5418 ME (8/18)

No further information

No references

Loco-regional Recurrence Prognostic/Predictive factors (9/18)

No further information

References:

Parameters in local recurrence to define risk for re-recurrence

Statement: Tumour size

1. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. 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, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. 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, Tsou MH, Tsai SY, Chen CM, Jian JJ, Liu MC, West M, Huang AT, Prosnitz LR. 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, Mamounas EP, Robidoux A, Martín M, Nortier JW, Geyer CE Jr, Paterson AH, Láng I, Price KN, Coates AS, Gelber RD, Rastogi P, Regan MM, Wolmark N, Aebi S; CALOR trial investigators. Poor Prognosis After Second Locoregional Recurrences in the CALOR Trial. *Ann Surg Oncol*. 2017 Feb;24(2):398-406

Statement: Early vs. Late recurrence

1. Lee JS, Kim SI, Park HS, Lee JS, Park S, Park BW. 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, Garcia DM, Simpson JR, Fineberg B. 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, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N 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

LVSI/Grade/ERneg/close margins

Change from close margin to positive margin

1. Panet-Raymond V, Truong PT, Alexander C, Lesperance M, McDonald RE, Watson PH. Clinicopathological factors of the recurrent tumor to predict outcome in patients with ipsilateral breast tumor recurrence. *Cancer* 117:2035, 2011
2. Margin width and Re-excision in breast conservativ treatment. a Denish breast coopertive group of 11.900 women. A. Bodilson et all 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, Fischer D, Ward B, McKhann C. 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, Cheng AL, Chang KJ, Chia-Hsien Cheng J. 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 (10/18)

No further information

No references

Ipsilateral Recurrence after BCT - Surgery (11/18)

Further information:

Mastectomy is the current standard of care for ipsilateral recurrence of breast carcinoma. Some retrospective analyses showed that second conservative treatments for local relapse were feasible and gave results comparable to standard mastectomy. A repeat BCT demands tumor-free margins and an interstitial brachytherapy. However, the indication for second lumpectomy is restricted for suited patients (small-size, low-risk). As data from prospective randomized clinical trials are missing, an impaired regional tumor control (without disadvantages for overall survival) cannot be ruled out completely. In patients with distant metastases a local surgery is indicated in pain, endangered ulceration and in some cases for psychological reasons. SLNB after previous axillary surgery is technically feasible after breast conserving therapy, but since randomized trials support the value of systemic therapy for all patients with invasive LR, reoperative SLNB, although feasible, may not be necessary.

References:

Statement: Mastectomy (aim: R0)

1. Alpert TE, Kuerer HM, Arthur DW, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 63(3):845-51, 2005
2. Shin E, Suemasu K, Sonoo H, Taguchi T, Nishi T, Nishimura R, Haga S, Mise K, Kinoshita T, Murakami S, Yoshimoto M, Tsukuma H, Inaji H: Analysis of ipsilateral breast tumor recurrences after breast-conserving treatment based on the classification of true recurrences and new primary tumors. *Breast Cancer* 12(2):104-11, 2005
3. Kolben T, Schwarz TM, Goess C, Blume C, Degenhardt T, Engel J, Wuerstlein R, Ditsch N, Harbeck N, Kahlert S: Surgical management of ipsilateral breast tumor recurrence. *Int J Surg*. 2015 Nov;23(Pt A):141-6.
4. NCCN clinical practice Guidelines in oncology (NCCN guidelines) breast cancer Version 3.2015 NCCN.org

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

1. Intra M, Trifirò G, Viale G, Rotmensz N, Gentilini OD, Soteldo J, Galimberti V, Veronesi P, Luini A, Paganelli G, Veronesi U. 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, Edwards GK, Conway K, Giuliano AE. 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, Fey J, Borgen PI, Cody HS 3rd: 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, Nieuwenhuijzen GA, van de Poll-Franse LV, Roumen RM, Voogd AC. 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, Tartter PI, Rosenbaum Smith SM, Boolbol SK: Reoperative sentinel lymph node biopsy in patients with locally recurrent breast cancer. *Am J Surg* 194(4):491-3,2007
6. Maaskant-Braat AJ¹, Voogd AC, Roumen RM, Nieuwenhuijzen GA. 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 MS¹, Rusby JE, Agusti AA, MacNeill FA.: 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 CC¹, Christensen MH, Oldenbourg MH, Kjær C, Garne JP, Teilum D, Kroman N, Tvedskov TF. Sentinel Lymph Node Dissection in Locally Recurrent Breast Cancer. *Ann Surg Oncol.* 2015 Jan 7. [Epub ahead of print]
9. *Ann Surg Oncol.* 2015 Dec 7. [Epub ahead of print]
Reoperative Sentinel Lymph Node Biopsy is Feasible for Locally Recurrent Breast Cancer, But is it Worthwhile?
Ugras S1, Matsen C1,2, Eaton A3, Stempel M1, Morrow M1, Cody HS 3rd4.

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

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery (12/18)

Further information:

Because chest wall recurrences are not infrequently a marker of concurrent or future metastatic disease, local management with curative intent is advocated only after thorough re-staging.

References:

Statement: Curative situation: R0-resection

1. Mignano JE, Gage I, Piantadosi S, Ye X, Henderson G, Dooley WC: Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without 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, Ye X, Henderson G, Dooley WC: Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. Am J Clin Oncol 30(5):466-72, 2007
2. Pfannschmidt J, Geisbüsch P, Muley T, Hoffmann H, Dienemann H.: Surgical resection of secondary chest wall tumors. Thorac Cardiovasc Surg 53(4):234-9, 2005

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

Locoregional Recurrence after R0-Resection - Systemic Treatment (13/18)

Further information:

Systemic therapy after resected local recurrence (re-adjuvant) is associated with improved disease-free and overall survival. Endocrine treatment in hormone sensitive tumors improves disease free survival. The impact on overall survival has not been proven.

References:

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, Jungi WF, Thürlimann B, Cavalli F, Obrecht JP. 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, Guinebretière JM, Rochard F. 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, Garcia DM, Simpson JR, Fineberg B. 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 W, Recht A. 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, Cheng AL, Chang KJ, Chia-Hsien Cheng J. 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, Láng I, Robidoux A, Martín M, Nortier JW, Paterson AH, Rimawi MF, Cañada JM, Thürlimann B, Murray E, Mamounas EP, Geyer CE Jr, Price KN, Coates AS, Gelber RD, Rastogi P, Wolmark N, Wapnir IL; CALOR investigators. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol.* 2014 Feb;15(2):156-63.

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, Kyriakides S, Senkus E; 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 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL; http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf

Chemo Therapy by Loco-regional Recurrence (14/18)

No further information

No references

Locoregional Recurrence in Case R0-resection not likely - Systemic Treatment (15/18)

No further information

References:

Statement: Endocrine therapy in endocrine responsive disease

1. Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M, Jungi WF, Thürlimann B, Cavalli F, Obrecht JP. 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, Guinebretière JM, Rochard F. 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, Garcia DM, Simpson JR, Fineberg B. 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, Tokuka A, Ohsumi K.: 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, Recht A. Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4)
5. Kuo SH, Huang CS, Kuo WH, Cheng AL, Chang KJ, Chia-Hsien Cheng J. Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17Version 3.2012
7. F. Cardoso ,A. Costa , E. Senkus , M. Aapro, F. Andre, C.H. Barrios , J. Bergh, G. Bhattacharyya , L. Biganzoli , M.J. Cardoso , L. Carey , D. Corneliussen-James , G. Curigliano , V. Dieras , N. El Saghir , A. Eniu , L. Fallowfield , D. Fenech , P. Francis , K. Gelmon , A. Gennari, N. Harbeck , C. Hudis , B. Kaufman, I. Krop , M. Mayer , H. Meijer , S. Mertz , S. Ohno , O. Pagani , E. Papadopoulos , F. Peccatori , F. Penault-Llorca , M.J. Piccart , J.Y. Pierga , H. Rugo , L. Shockney , G. Sledge , S. Swain , C. Thomssen , A. Tutt , D. Vorobiof , B. Xu , L. Norton , E. Winer. 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

So far, extrapolations from adjuvant HER2-directed studies and from studies in metastatic breast cancer. It needs to be emphasized that in some of the registration studies such as CLEOPATRA locally advanced, not operable tumors had been included.

Ipsilateral recurrence after BCT - Radiotherapy (16/18)

Further information:

Repeat irradiation breast for recurrent breast cancer is feasible. If no prior radiotherapy has performed after BCS, whole breast radiation should be performed. In patients with no prior radiotherapy after mastectomy irradiation of chest wall and regional lymph nodes is recommended.

References:

Statement: Whole breast radiation

1. McCready DR, Fish EB, Hiraki GY, Ross TM, Wall JL, Lickley HL. 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 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL; http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf
3. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; 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, Lannin DR, Haffty BG.: Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 63(3):845-51, 2005
4. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; 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

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

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: 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, Beckmann MW, Fietkau R. 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, Gomez S, Bodis S. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. *Int J Radiat Oncol Biol Phys.* 2016 Apr 1;94(5):1073-87.

3. Oldenburg S, Valk C, van Os R, Oei B, Venselaar J, Vörding PZ, van Randen A, Crezee H, van Tienhoven G, Rasch C. Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. *Strahlenther Onkol.* 2016 Apr;192(4):240-7.

Chest-wall recurrence / Axillary recurrence - radiotherapy (17/18)

No further information

References:

Statement: If no prior postmastectomy radiotherapy

1. Wahl AO, Rademaker A, Kiel KD, Jones EL, Marks LB, Croog V, McCormick BM, Hirsch A, Karkar A, Motwani SB, Tereffe W, Yu TK, Sher D, Silverstein J, Kachnic LA, Kesslering C, Freedman GM, Small W Jr: 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, Dewhurst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL.: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, Beckmann MW, Fietkau R. 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, Gomez S, Bodis S. 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. Oldenburg S, Valk C, van Os R, Oei B, Venselaar J, Vörding PZ, van Randen A, Crezee H, van Tienhoven G, Rasch C. Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. Strahlenther Onkol. 2016 Apr;192(4):240-7.

Statement Axillary recurrence

1. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Chapter Systemic treatment of recurrent or stage IV-breast cancer. BINV-17;Version 3.2012
2. Konkin DE, Tyldesley S, Kennecke H, Speers CH, Olivotto IA, Davis N 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

Loco-Regional Recurrence - Treatment Options in Non-Curative Cases (18/18)

Further information:

The combination of chemotherapy and hyperthermia (HT) is a promising approach in the treatment of malignant tumors. Local hyperthermia combined with radiotherapy may be effective in the treatment of locally recurrent breast cancer, especially for previously irradiated cases, where only a reduced total irradiation dose is applicable. Care should be taken, to select experienced providers that treat accordingly to recognised guidelines. While the combination of hyperthermia and radiotherapy has been used for several decades and shown its efficacy in prospective randomized trials, the combination of chemotherapy and hyperthermia (HT) has much less intensively been studied in breast cancer. Few recent papers report on trimodal therapeutic attempts: chemotherapy, radiotherapy plus hyperthermia, the additional benefit of chemotherapy is not quite clear.

References:

Statement: Concomitant radio-chemotherapy

1. McCormick 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

Statement: Hyperthermia + radiotherapy +/- chemotherapy

1. McCormick 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, Costa S: 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. Oldenburg S, Van Os RM, Van rij CM, Crezee J, Van de Kamer JB, Rutgers EJ, Geijssen ED, Zum vörde sive vörding PJ, Koning CC, Van tienhoven G.: 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, Lan L, McCall L, Dewhirst MW, Craciunescu O, Stauffer P, Liotcheva V, Betof A, Blackwell K. . 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. Kouloulis VE, Koukourakis GV, Petridis AK, Kouvaris I, Gouliamos AD. The efficacy of caelyx and hyperthermia for anticancer treatment. *Recent Pat Anticancer Drug Discov* 2(3):246-50, 2007
9. Kouloulis VE, Dardoufas CE, Kouvaris JR, Gennatas CS, Polyzos AK, Gogas HJ, Sandilos PH, Uzunoglu NK, Malas EG, Vlahos LJ. 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, Vesely H, Mahlmann B, Richter E. 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, Wiggeraad 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

Statement: Intraarterial chemotherapy

1. Murakami M, Kuroda Y, Nishimura S, Sano A, Okamoto Y, Taniguchi T, Nakajima T, Kobashi Y, Matsusue S. 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, Snider W, Dougherty D. 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, Hornung R, Walt H, Degen A, Fehr M. 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, Mocellin S, Basso M, Corti L, Balestrieri N, Marchet A, Rossi CR. The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. *Breast Cancer Res Treat* 134(3):1169-78, 2012
2. Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. *Acta Oncol* 51(6):713-21, 2012
3. Sersa G, Cufer T, Paulin SM, Cemazar M, Snoj M. *Cancer Treat Rev*. Electrochemotherapy of chest wall breast cancer recurrence 38(5):379-86, 2012