

# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Loco-Regional Recurrence



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## Loco-regional Recurrence

- **Versionen 2002–2018:**  
**Audretsch / Bauerfeind / Brunnert / Budach /  
 Costa / Dall / Fehm / Fersis / Friedrich / Harbeck /  
 Gerber / Göhring / Hanf / Lisboa / Kühn/ Maass /  
 Mundhenke / Rezai / Simon / Solomayer / Souchon /  
 Thomssen / Wenz**
  
- **Version 2019:**  
**Dall / Wöckel**

### Screened data bases

Pubmed 2005 - 2018, ASCO 2005 – 2018, SABCS 2009 – 2018, Cochrane data base

### Guidelines

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


Cardoso F, Costa A, Norton L et al; ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast. 2014 Oct;23(5):489-502.

Lin NU, Thomssen C, Cardoso F et al; European School of Oncology-Metastatic Breast Cancer Task Force. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: Surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013 Jun;22(3):203-10.

NCCN (National Comprehensive Cancer Network, 2012); [http://www.nccn.org/professionals/physician\\_gls/PDF/breast.pdf](http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf) (download 13. Jan. 2013)

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](http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf)

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

<div>  <div> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div> </div> <h2>Loco-regional Recurrence Incidence and Prognosis</h2>		
Localization	Frequency (%)	5-y. Overall Survival (%)
<b>Ipsilateral recurrence<sup>1</sup></b> (post BOT + irradiation)	10 (2–20)	65 (45–79)
<b>Chest wall<sup>1</sup></b> (post mastectomy)	4 (2–20)	50 (24–78)
<b>As above plus supraclavicular fossa<sup>2</sup></b>		
<b>Axilla:</b>	34%	49% (3-y. OS)
After ALND <sup>3</sup>	1 (0.1–8)	55 (31–77)
After SNB <sup>4</sup>	1	93%
<b>Multiple localizations<sup>2</sup></b>	16 (8–19)	21 (18–23)
<p><sup>1</sup> Haffty et al. Int J Radiat Oncol Biol Phys 21(2):293-298, 1991;</p> <p><sup>2</sup> Reddy JP. Int J Radiat Oncol Biol Phys 80(5):1453-7, 2011;</p> <p><sup>3</sup> Karabali-Dalamaga S et al. Br Med J 2(6139):730-733,1978;</p> <p><sup>4</sup> Andersson Y, et al. Br J Surg 99(2):226-31,2012</p>		

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2. Reddy JP, Levy L, Oh JL et al; Long-term outcomes in patients with isolated supraclavicular nodal recurrence after mastectomy and doxorubicin-based chemotherapy for breast cancer. Int J Radiat Oncol Biol Phys 80(5):1453-7, 2011
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5. Lowery AJ<sup>1</sup>, Kell MR, Glynn RW et al; Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012 Jun;133(3):831-41. doi: 10.1007/s10549-011-1891-6. Epub 2011 Dec 7.
6. [www.tumorregister-muenchen.de](http://www.tumorregister-muenchen.de)

	Oxford		
	LoE	GR	AGO
<b>Examinations before treatment</b>			
■ Tissue biopsy	5	D	++
■ Re-assessment of ER, PgR, HER2	3b	B	++
■ Complete re-staging	5	D	++
■ „Liquid biopsy“	5	D	-




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

 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Risk Factors for Loco-Regional Recurrence at Primary Diagnosis	
	Increased risk for loco-regional recurrence	
	<ul style="list-style-type: none"> <li>Young age</li> <li>Positive microscopic margins (R1) of the primary tumor</li> <li>Omitting adjuvant radiotherapy (if indicated)</li> <li>Extensive intraductal component</li> <li>Vessel invasion</li> <li>HER2 positive and triple negative &gt; Luminal B-like &gt; luminal A-like</li> <li>Number of involved lymph nodes</li> <li>Grading (G3)</li> <li>Elevated proliferation markers: e.g. Ki67;</li> <li>pT (&gt; 2)</li> <li>* nodal negativ</li> <li>Inflammatory breast cancer</li> <li>Medial tumor localisation</li> <li>Obesity (Body mass index)</li> </ul>	<p>Oxford LoE</p> <p>1a</p> <p>1a</p> <p>1a</p> <p>1b</p> <p>1b</p> <p>2a</p> <p>1a</p> <p>1b*</p> <p>2b</p> <p>1b*</p> <p>1a</p> <p>2b</p> <p>4</p> <p>1a</p>

#### Informative for the whole list of factors

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

#### Statement: Increased risk for loco-regional recurrence

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087–2106, 2005
2. Dalberg K, Mattsson A, Rutqvist LE et al; Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. Breast Cancer Res Treat 43: 73–86, 1997
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#### Statement: Young age

1. van der Hage JA, Mieog JS, van de Velde CJ et al; Impact of established prognostic factors and molecular subtype in very young breast cancer patients: pooled analysis of four EORTC randomized controlled trials. *Breast Cancer Res* 24;13(3):R68, 2011
2. Algara López M, Sanz Latiesas X, Foro Arnalot P et al; Risk factors of local relapse in breast cancer: the importance of age. *Clin Transl Oncol* 9(2):110-6, 2007
3. de Bock GH, van der Hage JA, Putter H et al; Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 42(3):351-6. 2006
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conservative surgery and radiation therapy. Eur J Cancer 37: 1820–1827, 2001

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#### Statement: Positive microscopic margins

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4. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
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patients treated over a 28-year period. Breast Cancer Res Treat. 2016 Apr;156(2)

7. Dixon JM, Thomas J, Kerr GR et al; A study of margin width and local recurrence in breast conserving therapy for invasive breast cancer. Eur J Surg Oncol. 2016 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 et al; Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. Breast Cancer Res Treat 43: 73–86, 1997
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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
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3. Wallgren A, Bonetti M, Gelber RD et al; Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 21: 1205–1213, 2003
4. Truong PT, Yong CM, Abnoui F et al; Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy. J Am Coll Surg. 200(6):912-21, 2005

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

1. van der Hage JA, Mieog JS, van de Velde CJ et al; Impact of established prognostic factors and molecular subtype in very young breast cancer patients:pooled analysis of four EORTC randomized controlled trials. *Breast Cancer Res Breast Cancer Res* 24;13(3):R68, 2011
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3. Dalberg K, Mattsson A, Rutqvist LE et al; Breast conserving surgery for invasive breast cancer: risk factors for ipsilateral breast tumor recurrences. *Breast Cancer Res Treat* 43: 73–86, 1997
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10. Lai SF, Chen YH, Kuo WH et al; Locoregional Recurrence Risk for Postmastectomy Breast Cancer Patients With T1-2 and One to Three Positive Lymph Nodes Receiving Modern Systemic Treatment Without Radiotherapy. *Ann Surg Oncol.* 2016 Nov;23(12):3860-3869.
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12. Jwa E, Shin KH, Kim JY et al; Locoregional Recurrence by Tumor Biology in Breast Cancer Patients after Preoperative Chemotherapy and Breast Conservation Treatment. *Cancer Res Treat*. 2016 Oct;48(4):1363-1372. Epub 2016 Feb 18.

Statement: Grading G3

1. de Bock GH, van der Hage JA, Putter H et al; Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 42(3):351-6, 2006
2. Cheng SH, Horng CF, Clarke JL et al; Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. *Int J Radiat Oncol Biol Phys* 64(5):1401-9, 2006
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
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12. *Breast Cancer.* 2014 May;21(3):292-301. doi: 10.1007/s12282-012-0391-9. Epub 2012 Aug 14.
13. Nagao T, Kinoshita T, Tamura N et al; Locoregional recurrence risk factors and the impact of postmastectomy radiotherapy on patients with tumors 5 cm or larger.

Statement: pN (N1 vs. N0)

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366: 2087–2106, 2005
2. [www.tumorregister-muenchen.de](http://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

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6. 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
7. Truong PT, Jones SO, Kader HA et al; Patients with t1 to t2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. *Int J Radiat Oncol Biol Phys* 73(2):357-64, 2009
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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 et al; Tumor location, interval between surgery and radiotherapy and boost technique influence local control after breast conserving surgery and radiation: retrospective analysis of monoinstitutional long-term results. *Int J Radiat Oncol Biol Phys* 72: 1048-55, 2008

Statement: elevate proliferation marker, esp. Ki67

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

#### Statement: Inflammatory breast cancer

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

#### Statement: 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. 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 et al; Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies. Sci Rep. 2014 Dec 15;4:7480.
3. Bergom C, Kelly T, Bedi M et al; Association of Locoregional Control With High Body Mass Index in Women Undergoing Breast Conservation Therapy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016 Sep 1;96(1):65-71
4. Warren LE, Ligibel JA, Chen YH et al; Body Mass Index and Locoregional Recurrence in Women with Early-Stage Breast Cancer. Ann Surg Oncol. 2016 Nov;23(12):3870-3879.

#### Recent evidence for Multigene arrays predicting risk for local relapse

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pooled analysis. Breast Cancer Res Treat. 2014 Dec;148(3):599-613.

2. Drukker CA, Elias SG, Nijenhuis MV et al; Erratum to: Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. Breast Cancer Res Treat. 2015 Jan 21.
3. Fitzal F, Filipits M, Fesl C et al; Predicting local recurrence using PAM50 in postmenopausal endocrine responsive breast cancer patients. J Clin Oncol 32:5s, 2014 (suppl; abstr 1008)



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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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## 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 BET 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			
	Oxford		
	LoE	GR	AGO
<b>Parameters of the locally recurrent tumor to define the risk for re-recurrence</b>			
▪ Tumor size	2a	B	
▪ Multifocality	2a	B	
▪ Localisation	2b	B	
▪ Negative progesterone receptor	3b	B	
<b>Parameters of the locally recurrent tumor to define the risk for distant metastasis/survival</b>			
▪ Early (< 2-3 yrs.) vs. late recurrence	2b	B	
▪ LVI / Grade / ER-neg / positive margins (if ≥ 2 factors positive)	3b	B	
<b>Predictive factors for treatment considerations</b>			
▪ HER2	2b	B	++
▪ ER and PgR	2b	B	++

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## Parameters in local recurrence to define risk for re-recurrence

### Statement: Tumour size

1. Wapnir IL, Anderson SJ, Mamounas EP et al; Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-37, 2006
2. Lannin DR, Haffty BG; End results of salvage therapy after failure of breast-conservation surgery. Oncology (Huntingt) 18(3):272-9, 2004 discussion 280-2, 285-6, 292.

### Statement: Multifocality

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

#### Statement: Localisation

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

#### Statement: ER-pos/PgR-pos vs ER-pos/PgR-neg or ER-neg/PgR-neg

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

#### Statement: Early vs. Late recurrence

1. Lee JS, Kim SI, Park HS et al; The impact of local and regional recurrence on distant metastasis and survival in patients treated with BCT. J Breast Cancer 14:191-7, 2011
2. Halverson KJ, Perez CA, Kuske RR et al; Survival following locoregional recurrence of breast cancer: univariate and multivariate analysis. Int J Radiat Oncol Biol Phys 23(2):285-91, 1992
3. Wapnir IL, Anderson SJ, Mamounas EP et al; Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol 4(13):2028, 2006

#### 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 Denish breast coopertive group of 11.900 women.

1. A. Bodilson et al; St Antonio Breast cancer symposium Dez.2015. Increased risk of IBTR associated with final positive margin.

Predictive factors for treatment considerations

Statement: HER-2

1. Clemons M, Hamilton T, Goss P; Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001

Statement: ER and PR

1. Clemons M, Hamilton T, Goss P; Does treatment at the time of locoregional failure of breast cancer alter prognosis? Cancer Treat Rev 27(2): 83–97, 2001
2. Haffty BG, Reiss M, Beinfield M et al; Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. J Clin Oncol 14: 52–57, 1996
3. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Oncology Biol Phys 72: 1456-64, 2008

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


**Panet-Raymond V et al. Cancer 117:2035, 2011**

n = 6020 pts., retrospective cohort-study  
pT1/2, N0 tumors, breast conserving treatment  
269 ipsilateral breast tumor recurrences (IBTR)

**Multivariate analysis:**

TTR < 48 months  
LVSI (of the LRR)  
ER negative LR-tumor  
high grade  
close margins of recurrent tumor

→ if  $\geq 2$  factors positive  $\Rightarrow$  worse OS



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## Ipsilateral Recurrence after BCT Surgery

Oxford		
LoE	GR	AGO
3b	B	++
3	C	+/-
4	C	-
2a	B	-
5	D	+

- **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)**

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

### Statement: Mastectomy (aim: R0)

1. Alpert TE, Kuerer HM, Arthur DW et al; Ipsilateral breast tumor recurrence after breast conservation therapy: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. Int J Radiat Oncol Biol Phys 63(3):845-51, 2005
2. Shin E, Suemasu K, Sonoo H et al; Analysis of ipsilateral breast tumor recurrences after breast-conserving treatment based on the classification of true recurrences and new primary tumors. Breast Cancer 12(2):104-11, 2005
3. Kolben T, Schwarz TM, Goess C et al; Surgical management of ipsilateral breast tumor recurrence. Int J Surg. 2015 Nov;23(Pt A):141-6.
4. NCCN clinical practice Guidelines in oncology (NCCN guidelines) breast cancer Version 3.2015 NCCN.org


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

1. Intra M, Trifirò G, Viale G et al; Second biopsy of axillary sentinel lymph node for reappearing breast cancer after previous sentinel lymph node biopsy. Ann Surg Oncol 12(11):895- 899, 2005

2. Taback B, Nguyen P, Hansen N et al; Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. *Ann Surg Oncol* 13(8):1099-104, 2006
3. Port ER, Garcia-Etienne CA, Park J et al; Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. *Ann Surg Oncol.* 14(8):2209-14, 2007
4. Derkx F, Maaskant-Braat AJ, van der Sangen MJ et al; Staging and management of axillary lymph nodes in patients with local recurrence in the breast or chest wall after a previous negative sentinel node procedure. *Eur J Surg Oncol* 36(7):646-51, 2010
5. Barone JL, Feldman SM, Estabrook A et al; Reoperative sentinel lymph node biopsy in patients with locally recurrent breast cancer. *Am J Surg* 194(4):491-3,2007
6. Maaskant-Braat AJ, Voogd AC, Roumen RM et al; Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat.* 2013 Feb;138(1):13-20. doi: 10.1007/s10549-013-2409-1. Epub 2013 Jan 23
7. Kothari MS, Rusby JE, Agusti AA et al; Sentinel lymph node biopsy after previous axillary surgery: A review. *Eur J Surg Oncol.* 2012 Jan;38(1):8-15. doi: 10.1016/j.ejso.2011.10.003. Epub 2011 Oct 26.
8. Uth CC, Christensen MH, Oldenbourg MH et al; Sentinel Lymph Node Dissection in Locally Recurrent Breast Cancer. *Ann Surg Oncol.* 2015 Jan 7. [Epub ahead of print]
9. Ugras S, Matsen C, Eaton A et al; Reoperative sentinel lymph node biopsy is feasible for locally recurrent breast cancer, but is it worthwhile? *Ann Surg Oncol.* 2016 March ; 23(3): 744–748. doi:10.1245/s10434-015-5003-4.

#### 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

	Oxford		
	LoE	GR	AGO
<div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2019.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div>	<h2>Chest-Wall Recurrence after Mastectomy / Axillary Recurrence - Surgery</h2>		
<ul style="list-style-type: none"> <li>Curative situation: R0-resection (including deeper parts of the chest wall in selected cases: HR pos, primary N-)</li> </ul>	2b	A	++
<ul style="list-style-type: none"> <li>Palliative situation: Resection of deep parts of the chest wall</li> </ul>	5	D	+/-
<ul style="list-style-type: none"> <li>Palliative surgery in M1-situation (e.g. pain, ulceration, psychosocial)</li> </ul>	5	D	+
<ul style="list-style-type: none"> <li>SLNE after prior SLNE if cN0*</li> </ul>	3b	B	-

### Statement: Curative situation: R0-resection

1. Mignano JE, Gage I, Piantadosi S et al; 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 et al; 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 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

### 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: Ugras et al., Annals of Surgical Oncol 23: 744-8, 2016



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## Loco-regional Recurrence after R0-Resection Systemic Treatment

	Oxford		
	LoE	GR	AGO
<b>According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)</b>			
▪ 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	+

### Statement: Endocrine therapy in endocrine responsive disease

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

### Statement: Chemotherapy

1. Easson AM, McCready DR; Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
2. Rauschecker H, Clarke M, Gatzemeier et al; Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4):CD002195. Review.

3. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008.
4. Aebi S, Gelber S, Anderson SJ et al; CALOR investigators. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol. 2014 Feb;15(2):156-63.
5. Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406

Statement: Trastuzumab - based therapy in HER-2 overexpressing tumors

1. So far, extrapolations from adjuvant HER2-directed studies and from studies in metastatic breast cancer  
Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22:suppl 7:vii11-9, 2012
2. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms  
Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL;  
[http://www.dggg.de/fileadmin/public\\_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf](http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf)

## Chemo Therapy by Loco-regional Recurrence

### ■ CALOR Trial update

**n = 163 (2003-2010), median follow-up of 4.9 years, all R0 resection**

**5-year disease-free survival: 69% (95% CI 56-79) with chemotherapy  
vs. 57% (44-67) without chemotherapy (hazard ratio 0.59  
[95% CI 0.35-0.99]; p=0.046): 24 (28%) patients vs. 34 (44%).**

**Adjuvant chemotherapy was significantly more effective in  
ER negative disease ( $p_{\text{interaction}}=0.046$ ).**

**Multivariate analysis: predictors of survival**

**chemotherapy for primary cancer (HR 3.55, p=0.03)**

**interval from primary surgery (HR 0.87, p=0.05)**

Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406 | Cite as

# Chemotherapie bei lokoregionärem Rezidiv

## ■ CALOR Trial update

Endpoint	ER-positive			ER-negative		
	CT	No-CT	HR (95%CI)	CT	No-CT	HR (95%CI)
10-yr DFS	50%	59%	1.07 (0.57 – 2.00)	70%	34%	0.29 (0.13 – 0.67)
Interaction P-Value =0.013						
10-yr OS	76%	66%	0.70 (0.32 – 1.55)	73%	53%	0.48 (0.19 – 1.20)
Interaction P-value =0.53						
10-yr BCFI	58%	62%	0.94 (0.47 – 0.85)	70%	34%	0.29 (0.13 – 0.67)
Interaction P-value = 0.034						

Wapnir IL et al. Annals of Surgical Oncology, February 2017, Volume 24, Issue 2, pp 398–406| Cite as

Locoregional Recurrence in Case of R1-Resection/Inoperability – Systemic Treatment			
	Oxford		
	LoE	GR	AGO
<b>According to pathohistological re-evaluation of the recurrent tumor (ER, PgR, HER2)</b>			
▪ 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	++

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#### Statement: Endocrine therapy in endocrine responsive disease

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


#### Statement: Chemotherapy (pre- or postoperatively)

1. Kuo SH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiat Oncol Biol Phys 72: 1456-64 (2008)
2. Tokunaga Y, Hosogi H, Nakagami M et al; A case of chest wall recurrence of breast cancer treated with paclitaxel weekly, 5'-deoxy-5-fluorouridine, arterial embolization and chest wall resection. Breast Cancer. 2003;10(4):366-70.

3. Easson AM, McCready DR; Management of local recurrence of breast cancer. Expert Rev Anticancer Ther 4(2):219-26, 2004
4. Rauschecker H, Clarke M, Gatzemeier W et al; Systemic therapy for treating locoregional recurrence in women with breast cancer. Cochrane Database Syst Rev. 2001;(4)
5. Kuo SH, Huang CS, Kuo WH et al; Comprehensive locoregional treatment and systemic therapy for postmastectomy isolated locoregional recurrence. Int J Radiation Oncology Biol Phys 72: 1456-64, 2008
6. [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](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 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

Ipsilateral Recurrence after BCT Radiotherapy			
	Oxford		
	LoE	GR	AGO
<b>After Re-BCS</b>			
▪ Whole breast irradiation (in case adjuvant radiotherapy was not performed)	3b	C	++
▪ Re-breast irradiation (Partial breast radiation, brachytherapy, external beam RT)	3b	C	+/-
<b>After mastectomy</b>			
▪ Radiation of chest wall +/- regional lymph nodes (14% involved supraclavicular metastasis)	2b	B	+/-
▪ Radiation dose escalation (+10%)	3b	C	-
▪ Repeated irradiation (e.g. as brachytherapy) with hyperthermia	3a	C	+


  
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#### 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 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032 – 045OL; [http://www.dggg.de/fileadmin/public\\_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf](http://www.dggg.de/fileadmin/public_docs/Leitlinien/S3-Brustkrebs-v2012-OL-Langversion.pdf)
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: outcomes of salvage mastectomy vs. salvage breast-conserving surgery and prognostic factors for salvage breast preservation. *Int J Radiat Oncol Biol Phys* 63(3):845-51, 2005
4. Cardoso F, Harbeck N, Fallowfield L et al; ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 22:suppl 7:vii11-9, 2012
5. Skinner HD, Strom EA, Motwani SB et al; Radiation dose escalation for locoregional recurrence of breast cancer after mastectomy. *Radiat Oncol* 8: 13, 2013
6. Linthorst M, van Geel AN, Baaijens M et al; Re-irradiation and hyperthermia after pulsed dose rate (PDR) brachytherapy moulds for breast cancer local recurrences. *Int J Radiat*
7. Surgery for recurrent breast cancer . *Radiother Oncol* 2013;109:188-93
8. Linthorst M, van Geel AN, Baartman EA et al; Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. *Strahlenther Onkol* 2013;189:387-393
9. Datta NR et al; Hyperthermia and radiation therapy in locoregional recurrent breast cancer: A systematic review and metaanalysis. *Int J Rad Oncol* 94:1073-87 (2016)

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

1. Wahl AO, Rademaker A, Kiel KD et al; Multi-Institutional Review of Repeat Irradiation of Chest Wall and Breast for Recurrent Breast Cancer. *Int J Radiat Oncol Biol Phys*. 2007 Sep 13

Statement Re-Irradiation of the chest wall with hyperthermia

1. Auoragh A, Strnad V, Ott OJ et al; Re-irradiation of the chest wall for local breast cancer recurrence : Results of salvage brachytherapy with hyperthermia. *Strahlenther Onkol*. 2016 Sep;192(9):617-23.

2. Datta NR, Puric E, Klingbiel D et al; Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. *Int J Radiat Oncol Biol Phys.* 2016 Apr 1;94(5):1073-87.
3. Oldenburg S, Valk C, van Os R et al; Rib fractures after reirradiation plus hyperthermia for recurrent breast cancer: Predictive factors. *Strahlenther Onkol.* 2016
4. Oldenburg S, et al., Re-Irradiation und hyperthermia for recurrent breast cancer en cuirasse. *Strahlentherapie und Onkologie* 194: 206-214, 2018

Chest-Wall Recurrence after Mastectomy / Axillary Recurrence Radiotherapy			
	Oxford		
	LoE	GR	AGO
<b><u>Chest-Wall Recurrence (R0-Resection) after Mastectomy</u></b>			
▪ If no prior postmastectomy radiotherapy			
▪ Curative situation: irradiation of the chest wall +/- regional lymph nodes	2b	B	+
▪ Re-irradiation (chest wall + hyperthermia)	1b	B	+/-
<b><u>Axillary Recurrence</u></b>			
▪ Irradiation of axilla after R0-surgery			
▪ No prior adjuvant irradiation of the axilla	3b	C	+
▪ Adjuvant irradiation of the axilla	5	D	+/-

#### 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. [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](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 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



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## Loco-Regional Recurrence

### Treatment Options in Non Curative Cases

	Oxford		
	LoE	GR	AGO
■ Concomitant radio-chemotherapy	<b>3b</b>	<b>C</b>	<b>+</b>
■ Hyperthermia (in centers listed on DKG website)			
■ In combination with radiotherapy	<b>1b</b>	<b>B</b>	<b>+</b>
■ In combination with chemotherapy	<b>4</b>	<b>C</b>	<b>+/-</b>
■ Intra-arterial chemotherapy	<b>4</b>	<b>C</b>	<b>+/-</b>
■ Photodynamic therapy	<b>4</b>	<b>C</b>	<b>+/-</b>
■ Electrochemotherapy	<b>3b</b>	<b>C</b>	<b>+/-</b>

#### 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
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#### 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
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#### Statement: Intraarterial chemotherapy

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#### Statement: Photodynamic therapy

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

Statement: Electrochemotherapy

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