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

## Breast Cancer Surgery Oncological Aspects



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## Breast Cancer Surgery Oncological Aspects

### ■ Versions 2002–2023:

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Ditsch / Fallenberg / Fersis / Friedrich / Gerber / Hanf / Janni /  
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### ■ Version 2024


**Rody / Schütz**



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## Breast Cancer Surgery Oncological Aspects

**AGO: ++**  
Surgery is one sub-step out of multiple steps in breast cancer treatment. Thus, both diagnostic and oncological expertise are an essential requirement for every breast surgeon.

**AGO: +**  
Avoidance of a significant delay in cancer treatment

**AGO: ++**  
Surgical therapy decisions should be made in the context of a multimodal therapy concept; in particular, the waiver of diagnostic measures (e.g. SLNE) should be decided as part of a preoperative, interdisciplinary tumor conference.

### Delay of surgical therapy:

1. Hanna TP, King WD, Thibodeau S et al: Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ371:m4087
2. Cone EB, Marchese M, Paciotti M, et al: Assessment of Time-to-Treatment Initiation and Survival in a Cohort of Patients With Common Cancers. JAMA Netw Open. 2020;3(12):e2030072. doi: 10.1001/jamanetworkopen.2020.30072. PMID: 33315115; PMCID: PMC7737088.
3. Wiener, Hanlon, Schumacher et al., Reexamining Time From Breast Cancer Diagnosis to Primary Breast Surgery, JAMA Surg, 2023 May 1;158(5):485-492

### Surgeon:

1. Dixon JM, Grewar J, Twelves D, et al: Factors affecting the number of sentinel lymph nodes removed in patients having surgery for breast cancer. Breast Cancer Res Treat 184:335-343, 2020



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## Pre-therapeutic Assessment of Breast

	Oxford		
	LoE	GR	AGO
▪ <b>Clinical examination</b>	5	D	++
▪ <b>Mammography (completion of the imaging)</b>	2b	B	++
▪ + Tomosynthesis (DBT)***	2b	B	+
▪ Contrast-enhanced mammography (alone) adjusted with regards of radiation sensitivity of patient and availability*	2a	B	+
▪ <b>Sonography (breast<sup>†</sup>)</b>	2b <sup>†</sup>	B	++
▪ <b>MRI*</b>	1b	A	+
▪ <b>Minimally invasive biopsy**</b>	1b	A	++
▪ <b>Breast-CT</b>	4	D	-
▪ <b>Axillary PET (PET-CT, PET-MR)</b>	2b	B	-

- \* MRI- or CEM guided vacuum biopsy is mandatory in case of MRI- or CEM detected additional lesions (in house or with cooperations). Individual decision for patients at high familial risk, with dense breast (density C / D), lobular invasive tumors, suspicion of multilocular disease.
- \*\* Histopathology of additional lesions if relevant for treatment
- \*\*\* Replacement of additional FFDM with SM

### Combined DM + DBT + US + MRI

1. Mariscotti G, Houssami N, Durando M, et al. Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. *Anticancer Res.* 2014 Mar;34(3):1219-25.
2. Campanino PP, Ruggieri C, Regini E, et al. Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. *Anticancer Res.* 2014 Mar;34(3):1219-25.
3. Schünemann HJ, Lerda D, Quinn C, et al. Breast Cancer Screening and Diagnosis: A Synopsis of the European Breast Guidelines. *Annals of Internal Medicine.* 2020;172(1):46-56.

### US+FNA/CNB

1. Evans A, Trimboli RM, Athanasiou A et al. Breast ultrasound: recommendations for information to women and referring physicians by the European Society of Breast Imaging. *European of Breast Imaging (EUSOBI)* , with language review by Europa Donna–The European Breast Cancer Coalition. *Insights Imaging.* 2018 Aug;9(4):449-461. doi: 10.1007/s13244-018-0636-z. Epub 2018 Aug 9.

## Biopsie

1. Chan KY, WiseberdFirtell, J, Jois HSR, et al. Localisation techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database of Systematic reviews 2015;vol 12
2. Lourenco AP, Mainiero MB Incorporating imaging into the locoregional management of breast cancer. Semin Radiat Oncol 2016;26(1)
3. Mariscotti G, Houssami N, Durando M, et al. Accuracy of mammography, digital breast tomosynthesis, ultrasound and MR imaging in preoperative assessment of breast cancer. Anticancer Res. 2014 Mar;34(3):1219-25.

## MRT

1. Mann RM, Loo CE, Wobbles T et al The impact of preoperative MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat 2010; 119: 415-422
2. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. 2013 Feb;257(2):249-55.
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6. Houssami N, Turner R, Macaskill P, et al. An individual person data meta-analysis of preoperative magnetic resonance imaging and breast cancer recurrence. J Clin Oncol 2014;32(5):392-401
7. Vos EL, Voogd AC, Verhoef C, et al. Benefits of preoperative MRI in breast cancer surgery studied in a large population-based cancer registry. Br J Surg 2015;102(13)1649-1657
8. Lehman CD, Lee JM, DeMartini WS, et al. Screening MRI in women with a personal history of breast cancer. J Natl Cancer Inst 2016;108(3)

9. Wang SY, Long JB, Killelea BK, et al. Preoperative breast MRI and contralateral breast cancer occurrence among older women with breast cancer. *J Clin Oncol* 2015;Nov 30, epub ahead of print
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12. Vriens BE, de Vries B, Lobbes MB, et al. Ultrasound is at least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. *Eur J Cancer*. 2016 Jan;52:67-76.
13. Health Quality Ontario. Magnetic Resonance Imaging as an Adjunct to Mammography for Breast Cancer Screening in Women at Less Than High Risk for Breast Cancer: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2016; Nov 1;16(20):1-30
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15. Houssami N, Turner RM, Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. *Breast Cancer Res Treat*. 2017 Sep;165(2):273-283
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### Reviews CEM:

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7. The performance of contrast-enhanced mammography and breast MRI in local preoperative staging of invasive lobular breast cancer. Lobbes MBI, et al. *Eur J Radiol*. 2023. PMID: 37201248

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13. Sung JS, Lebron L, Keating D, et al. Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer. *Radiology*. 2019;293(1):81-8.
14. Preoperative staging by multimodal imaging in newly diagnosed breast cancer: Diagnostic performance of contrast-enhanced spectral mammography compared to conventional mammography, ultrasound, and MRI. Daniaux M, Gruber L, De Zordo T, Geiger-Gritsch S, Amort B, Santner W, Egle D, Baltzer PAT. *Eur J Radiol*. 2023 Jun;163:110838. doi: 10.1016/j.ejrad.2023.110838. Epub 2023 Apr 15. PMID: 37080064 Free article.
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Brust-CT:

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# Pre-therapeutic Assessment Axilla

	Oxford		
	LoE	GR	AGO
▪ <b>Clinical examination</b>	5	D	++
▪ <b>Mammography</b>	2b	B	-
▪ + Tomosynthesis***	2b	B	-
▪ CEM (alone) after unclear resection (Rx) if available	2a	B	-
▪ <b>Ultrasound (Axilla<sup>II</sup>)</b>	2a <sup>II</sup>	B	++
▪ <b>MRI</b>	1b	A	+
▪ <b>US-Axilla + FNA/CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤ 3 susp. LK</b>	2b	B	++

## US-Axilla + FNA/CNB Axilla, if suspicious LN and marking of the node if TAD planned ≤ 3 susp. LK

1. Diepstraten SC, Sever AR, Buckens CFM, et al. Value of preoperative ultrasound guided lymphnode biopsy for preventing completion axillary lymphnode dissection in breast cancer: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:51-59
2. Evans A, Rauchhaus P, Whelehan P, et al. Does shear wave ultrasound independently predict axillary lymph node metastasis in women with invasive breast cancer? Breast Cancer Res Treat. 2013 Dec 4. [Epub ahead of print]
3. Feng Y, Huang R, He Y, et al. Efficacy of physical examination, ultrasound, and ultrasound combined with fine-needle aspiration for axilla staging of primary breast cancer. Breast Cancer Res Treat. 2015 Feb;149(3):761-5. doi: 10.1007/s10549-015-3280-z. Epub 2015 Feb 10.
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8. Lehman CD, Lee JM, DeMartini WS, et al. Screening MRI in women with a personal history of breast cancer. *J Natl Cancer Inst* 2016;108(3)
9. Wang SY, Long JB, Killelea BK, et al. Preoperative breast MRI and contralateral breast cancer occurrence among older women with breast cancer. *J Clin Oncol* 2015;Nov 30, epub ahead of print
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4. Zhu, X., et al., Diagnostic Value of Contrast-Enhanced Spectral Mammography for Screening Breast Cancer: Systematic Review and Meta-analysis. *Clin Breast Cancer*, 2018. 18(5): p. e985-e995.
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5. Jochelson, M.S., et al., Comparison of screening CEDM and MRI for women at increased risk for breast cancer: A pilot study. *Eur J Radiol*, 2017. 97: p. 37-43.
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#### Brust-CT:

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## Pre-therapeutic Staging

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>History and clinical examination</li> </ul>	5	D	++
<b>Only in case of high metastatic potential and/or symptoms and/or indication for (neo-) adjuvant chemotherapy and/or antibody-therapy:</b>			
<ul style="list-style-type: none"> <li>CT scan of thorax / abdomen / pelvis</li> </ul>	2a	B	+
<ul style="list-style-type: none"> <li>Bone scan</li> </ul>	2b	B	+
<ul style="list-style-type: none"> <li>Chest X-ray</li> </ul>	5	C	+/-
<ul style="list-style-type: none"> <li>Liver ultrasound</li> </ul>	5	D	+/-
<ul style="list-style-type: none"> <li>Further investigation in case of additional suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)</li> </ul>	2a	B	+
<ul style="list-style-type: none"> <li>FDG-PET or FDG-PET-CT** FDG-PET-MRT**</li> </ul>	2b	B	+/-
<ul style="list-style-type: none"> <li>Whole body MRI</li> </ul>	4	C	+/-

\* Contrast enhanced ultrasound  
 \*\* especially in patients with high tumor stage (III) if available

### Statement: history and physical examination

1. GCP

### Statement: high metastatic potential / symptoms

1. Rutgers, EJ et al: Quality control in the locoregional treatment of breast cancer (2001) EJC 37: 447-453
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## Evidence of Surgical Procedure

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	LoE	GR
<ul style="list-style-type: none"> <li>▪ <b>Survival rates after lumpectomy + RT are at least equivalent to those after (modified) radical mastectomy</b></li> </ul>	<b>1a</b>	<b>A</b>
<ul style="list-style-type: none"> <li>▪ <b>Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy</b></li> </ul>	<b>2b</b>	<b>B</b>
<ul style="list-style-type: none"> <li>▪ <b>Conservation of the NAC (nipple areola complex) is an adequate surgical procedure, if R0 resection is achieved</b></li> </ul>	<b>2b</b>	<b>C</b>

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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1E</p> <p>In collaboration with:</p>  <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	<ul style="list-style-type: none"> <li>▪ <b>Wire-guided localization</b></li> <li>▪ <b>Wireless intraoperative ultrasound-guided localization*</b></li> <li>▪ <b>Other procedures:**</b> <ul style="list-style-type: none"> <li>Radar reflectors</li> <li>Magnetic marker***</li> <li>Paramagnetic markers***               <ul style="list-style-type: none"> <li>MagSeed™ (compared with wire localization)***</li> </ul> </li> <li>Radiofrequency-based markers (RFID)***</li> <li>Radionuclide-guided localization (ROLL)</li> <li>Radioactive seeds****</li> </ul> </li> </ul>	<p>1a</p> <p>1a</p> <p>2b</p> <p>2b</p> <p>1b</p> <p>2b</p> <p>1a</p> <p>1a</p>	<p>A</p> <p>A</p> <p>B</p> <p>B</p> <p>A</p> <p>B</p> <p>A</p> <p>A</p>	<p>++</p> <p>++</p> <p>+/-</p> <p>+/-</p> <p>+</p> <p>+/-</p> <p>+/-</p> <p>+/-</p>
	<p>* The lesion must be sonographically visualized by the same examiner pre- and intraoperatively in its whole extension. Adequate equipment and training of the surgeon are mandatory.</p>			
	<p>** according to approval</p>			
	<p>*** not suitable for MRI-based response assessment under NACT</p>			
	<p>**** not approved in Germany</p>			

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Radiofrequency-based markers (RFID): cohort studies (no RCTs available):

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ROLL: for RCTs see meta-analyses above




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## Localization Methods for non-Palpable Breast Cancer: a Meta-Analysis

**Athanasίου et al. Eur J Surg Onc 2021:**

- Meta-analysis of RCTs
- 18 studies with 3112 patients
- Pairwise and network meta-analysis

Ultrasound-guided surgery vs. wire-guided surgery:

- decreased positive margin both in the pairwise [OR = 0.19 (0.11, 0.35); P < 0.01] and network meta-analysis [OR = 0.19 (0.11, 0.60)]
- a statistically significant reduction in re-operation rate [OR = 0.19 (0.11, 0.36); P < 0.01] and operative time [MD = -4.24 (-7.85, -0.63); P = 0.02]

Ultrasound-guided surgery vs. ROLL / RSL:

- a statistically significant reduction in positive margin compared to ROLL [OR = 0.19 (0.11,0.6)] and RSL [OR = 0.26 (0.13, 0.52)]

**„Ultrasound-guided surgery has potential benefits in reduction of positive surgical margin, the rest of the techniques seem to have equivalent efficacy.“**

1. Athanasίου C, Mallidis E, Tuffaha H. Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis. Eur J Surg Oncol. 2021 Oct 11;S0748-7983(21)00751-4. doi: 10.1016/j.ejso.2021.10.001.

		Oxford		
		LoE	GR	AGO
<ul style="list-style-type: none"> <li><b>Invasive breast cancer without extensive intraductal component (EIC)*</b> <ul style="list-style-type: none"> <li><b>Aim: tumor-free margins ("no ink on tumor" is sufficient even in case of unfavorable tumor biology)</b> 2a A ++</li> <li><b>Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)</b> 2a B ++</li> </ul> </li> <li><b>Invasive breast cancer with EIC*</b> <ul style="list-style-type: none"> <li><b>Re-excision for invasive or non-invasive tumor cells reaching margin (final histology)</b> 2a B ++</li> <li><b>Re-excision in case of a close margin of the intraductal component (&lt; 2 mm on final histology)**</b> 2a B -</li> </ul> </li> </ul>				
<p>* No clear definition of EIC in the literature. Increased risk of local recurrence in case of EIC with at least twice the greatest dimension of the invasive tumor component (definition according to the German S3 guideline).</p> <p>** Individual approach with consideration of patient's age and tumor extent</p>				

Invasive cancer – margins:

1. Moran MS, Schnitt SJ, Giuliano AE et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol. 2014 May 10;32(14):1507-15. doi: 10.1200/JCO.2013.53.3935.
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Invasive cancer with intraductal component - margins:

1. Morrow M, Van Zee KJ, Solin LJ et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ. J Clin Oncol. 2016 Nov 20;34(33):4040-4046. doi: 10.1200/JCO.2016.68.3573.
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Statement: tumor free margins in intrinsic subtypes

1. Sioshansi S, Ehdaivand S, Cramer C, et al. Triple negative breast cancer is associated with an increased risk of residual invasive carcinoma after lumpectomy. Cancer. 2012 Aug 15;118(16):3893-8
2. Gangi A, Chung A, Mirocha J et al. Breast-conserving therapy for triple-negative breast cancer. JAMA Surg. 2014 Mar;149(3):252-8
3. Vaz-Luis I, Ottesen RA, Hughes ME, et al. Outcomes by tumor subtype and treatment pattern in women with small, node-negative breast cancer: a multi-institutional study. J Clin Oncol. 2014 Jul 10;32(20):2142-50.
4. Pilewski M, Ho A, Orell E, et al. Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast conserving therapy. Ann Surg Oncol. 2014 Apr;21(4):1209-14.


Statement: ... re-excision ...

1. Hennigs A, Fuchs V, Sinn HP et al. Do Patients After Reexcision Due to Involved or Close Margins Have the Same Risk of Local Recurrence as Those After One-Step Breast-Conserving Surgery? Ann Surg Oncol. 2016 Jun;23(6):1831-7. doi: 10.1245/s10434-015-5067-1
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4. Schouten van der Velden AP, Van de Vrande SL, Boetes C: Residual disease after re-excision for tumor-positive surgical margins in both ductal carcinoma in situ and invasive carcinoma of the breast: The effect of time. *J Surg Oncol.* 2007 Dec 1;96(7):569-74
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Extensive intraductal component:


1. Sinn HP, Anton HW, Magener A et al. Extensive and predominant in situ component in breast carcinoma: their influence on treatment results after breast-conserving therapy. *Eur J Cancer*, 1998. 34(5): p. 646- 53.
2. S3-Guideline Early Detection, Diagnosis, Treatment and Follow-up Care of Breast Cancer (Version 4.4, June 2021)
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## Breast-Conserving Surgery (BCS): Surgical and Technical Aspects

	Oxford		
	LoE	GR	AGO
▪ <b>Specimen radiography and / or -sonography in non-palpable lesions and / or tumor-associated microcalcifications*</b>	<b>2b</b>	<b>B</b>	<b>++</b>
▪ <b>Intraoperative ultrasound to increase negative margin rates in non-palpable lesions</b>	<b>1a</b>	<b>A</b>	<b>+</b>
▪ <b>Intraoperative ultrasound to increase negative margins rates in palpable lesions (with smaller resection volumes)</b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>Surgical clip marking of the tumor bed if boost or partial breast irradiation is indicated</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Intraoperative margin evaluation (with Margin Probe®)</b>	<b>1b</b>	<b>A</b>	<b>+/-</b>
▪ <b>Therapeutic stereotactic excision alone</b>	<b>4</b>	<b>D</b>	<b>--</b>

\* **Mandatory also for probe-guided detection systems (magnetic seeds, radar reflectors, RFID, radioactive seeds, ROLL)**

### Statement: stereotactic excision alone ...

1. Jackman RJ, Birdwell RL, Ikeda DM: Atypical ductal hyperplasia: can some lesions be defined as probably benign after stereotactic 11-gauge vacuum-assisted biopsy, eliminating the recommendation for surgical excision? *Radiology*. 2002 Aug;224(2):548-54
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3. Pan H, Wu N, Ding H, et al. Intraoperative Ultrasound Guidance Is Associated with Clear Lumpectomy Margins for Breast Cancer: A Systematic Review and Meta-Analysis. *PLOS One* 2013;8(9), e74028
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Intraoperative ultrasound: RCTs in non-palpable breast cancer:

1. Hu X, Si Li, Yi Jiang et al: Intraoperative ultrasound-guided lumpectomy versus wire-guided excision for nonpalpable breast cancer. *J Int Med Res* 48 (1):1-12, 2020
2. Hoffmann J, Marx M, Hengstmann A, et al:Ultrasound-Assisted Tumor Surgery in Breast Cancer - A Prospective, Randomized, Single-Center Study (MAC 001); *Ultraschall Med.* 2019 Jun;40(3):326-332. doi: 10.1055/a-0637-1725.
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Intraoperative ultrasound: RCTs in palpable breast cancer:

1. Volders JH, Haloua MH, Krekel NM et al. (2017) Intraoperative ultrasound guidance in breast-conserving surgery shows superiority in oncological outcome, long-term cosmetic and patient-reported outcomes: Final outcomes of a randomized controlled trial (COBALT). *Eur J Surg Oncol* 43:649-657. 10.1016/j.ejso.2016.11.004
2. Volders JH, Negenborn VL, Haloua MH, et al. (2018) Breast-specific factors determine cosmetic outcome and patient satisfaction after breast-conserving therapy: Results from the randomized COBALT study. *J Surg Oncol* 117:1001-1008. 10.1002/jso.25012
3. Krishna KL, Srinath BS, Santosh D, Velusamy S, Divyamala KP, Sariya Mohammadi J, Kurpad V, Kulkarni S, Yaji P, Goud S, Dhanireddy S, Ram J (2020) A comparative study of perioperative techniques to attain negative margins and spare healthy breast tissue in breast conserving surgery. *Breast Dis* 39:127-135. 10.3233/BD-200443
4. Vispute T, Suhani, Seenu V, et al. (2018) Comparison of resection margins and cosmetic outcome following intraoperative ultrasound-

guided excision versus conventional palpation-guided breast conservation surgery in breast cancer: A randomized controlled trial. Indian J Cancer 55:361-365. 10.4103/ijc.IJC\_2\_18

#### Margin probe:

1. Freya Schnabel, Susan K. Boolbol, Mark Gittleman, et al: A Randomized Prospective Study of Lumpectomy Margin Assessment with Use of MarginProbe in Patients with Nonpalpable Breast Malignancies Ann Surg Oncol (2014) 21:1589–1595
2. Geha RC, Taback B, Cadena L et al. A Single institution's randomized double-armed prospective study of lumpectomy margins with adjunctive use of the MarginProbe in nonpalpable breast cancers. Breast J. 2020 Nov;26(11):2157-2162. doi: 10.1111/tbj.14004.
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#### Specimen radiography/Specimen ultrasound:

1. Versteegden DPA, Keizer LGG, Schlooz-Vries MS et al. Performance characteristics of specimen radiography for margin assessment for ductal carcinoma in situ: a systematic review. Breast Cancer Res Treat. 2017 Dec;166(3):669-679. doi: 10.1007/s10549-017-4475-2
2. St John ER, Al-Khudairi R, Ashrafian H et al. Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-analysis. Ann Surg 2017 Feb;265(2):300-310. doi: 10.1097/SLA.0000000000001897.
3. Tan KY et al. Breast specimen ultrasound and mammography in the prediction of tumour-free margins. ANZ J Surg. 2006 Dec;76(12):1064-7.
4. Mazouni C, Rouzier R, Balleyguier C. Specimen radiography as predictor of resection margin status in non-palpable breast lesions. Clin Radiol. 2006 Sep;61(9):789-96.
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Breast Cancer Res Treat. 2020 Jan;179(2):425-433. doi: 10.1007/s10549-019-05476-6.

Intraoperative clip marking of the tumor bed:


1. van Mourik AM, Elkhuizen PHM, Minkema D et al.; Dutch Young Boost Study Group; Corine van Vliet-Vroegindeweij  
Multiinstitutional study on target volume delineation variation in breast radiotherapy in the presence of guidelines. *Radiother Oncol* 2010 Mar;94(3):286-91.
2. Hlavka A, Vanasek J, Odrázka K et al. Tumor bed radiotherapy in women following breast conserving surgery for breast cancer-safety margin with/without image guidance. *Oncol Lett*. 2018 Apr;15(4):6009-6014.
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4. Koch CA, Corey G, Liu ZA et al. Partial Breast Irradiation and Surgical Clip Usage for Tumor Bed Delineation After Breast-Conserving Surgery in Canada: A Radiation Oncology Perspective. *Adv Radiat Oncol*. 2021 Apr 20;6(4):100701. doi: 10.1016/j.adro.2021.100701. eCollection 2021 Jul-Aug. PMID: 34409206
5. Ebner F, de Gregorio N, Rempen A, To clip or not to clip the breast tumor bed? A retrospective look at the geographic miss index and normal tissue index of 110 patients with breast cancer. *J Turk Ger Gynecol Assoc*. 2017 Jun 1;18(2):67-71.



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## Breast-Conserving Surgery (BCS) without Neoadjuvant Therapy

Oxford		
LoE	GR	AGO
2b	B	+
2b	B	--
2b	B	--

- **Multifocality / Multicentricity  
(R0 resection of all lesions required)**
- **Positive microscopic margins after repeated excision**
- **Inflammatory breast cancer**

**For surgery after neoadjuvant chemotherapy see chapter  
„Neoadjuvant chemotherapy“**

### Statement: Multicentricity

1. Wolters R, Wöckel A, Janni W. et al; BRENDA Study Group. Comparing the outcome between multicentric and multifocal breast cancer: what is the impact on survival, and is there a role for guideline-adherent adjuvant therapy? A retrospective multicenter cohort study of 8,935 patients. Breast Cancer Res Treat. 2013 Dec;142(3):579-90.
2. Tan MP, Sitoh NY, Sim AS. Breast conservation treatment for multifocal and multicentric breast cancers in women with small-volume breast tissue. ANZ J Surg. 2014 Dec 5. doi: 10.1111/ans.12942.
3. Winters ZE, Horsnell J, Elvers KT et al. Systematic review of the impact of breast-conserving surgery on cancer outcomes of multiple ipsilateral breast cancers. BJS Open. 2018 May 22;2(4):162-174.
4. Masannat YA, Agrawal A, Maraqa L et al. Multifocal and multicentric breast cancer, is it time to think again? Ann R Coll Surg Engl. 2020 Jan;102(1):62-66.
5. Neri A, Marrelli D, Megha T et al. Clinical significance of multifocal and multicentric breast cancers and choice of surgical treatment: a retrospective study on a series of 1158 cases. BMC Surg. 2015 Jan 14;15:1.
6. Boughey JC, Rosenkranz KM, Ballman KV et al., Impact of breast conservation therapy on local recurrence in patients with multiple ipsilateral breast cancer - results from ACOSOG Z11102 (Alliance). SABCS 2022, GS4-01

Statement: positive microscopic margins

1. Houssami N, Macaskill P, Marinovich ML, et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014 Mar;21(3):717-30.
2. Marinovich ML, Azizi L, Macaskill P, et al: The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis. *Ann Surg Oncol*. 2016 Nov;23(12):3811-3821

Statement: Inflammatory Carcinoma

1. Coleman CN, Wallner PE, Abrams JS. Inflammatory breast issue. *J Natl Cancer Inst*. 2003 Aug 20;95(16):1182-3.
2. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. *Breast Dis*. 2005-2006;22:67-7
3. Woodward WA, Buchholz TA. The role of locoregional therapy in inflammatory breast cancer. *Semin Oncol*. 2008 Feb;35(1):78-86
4. Bristol IJ, Woodward WA, Strom EA, Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 2008 Oct 1;72(2):474-84.
5. Singletary SE Surgical management of inflammatory breast cancer. *Semin Oncol*. 2008 Feb;35(1):72-7
6. van Uden DJ, van Laarhoven HW, Westenberg AH et al. Inflammatory breast cancer: An overview. *Crit Rev Oncol Hematol*. 2015 Feb;93(2):116-26.
7. Matro JM, Li T, Cristofanilli M, Hughes ME, et al. Inflammatory breast cancer management in the national comprehensive cancer network: the disease, recurrence pattern, and outcome. *Clin Breast Cancer*. 2015 Feb;15(1):1-7.
8. Mamouch F, Berrada N, Aoullay Z et al. Inflammatory Breast Cancer: A Literature Review. *World J Surg*;9(5-6):129-135

Statement: general

1. Marret H, Perrotin F, Bognoux P. Histologic multifocality is predictive of skin recurrences after conserving treatment of stage I and II breast cancers. *Breast Cancer Res Treat*. 2001 Jul;68(1):1-8.
2. Cho LC, Senzer N, Peters GN. Conservative surgery and radiation therapy for macroscopically multiple ipsilateral invasive breast

cancers. *Am J Surg.* 2002 Jun;183(6):650-4.

3. Okumura S, Mitsumori M, Yamauchi C. Feasibility of breast-conserving therapy for macroscopically multiple ipsilateral breast cancer. *Int J Radiat Oncol Biol Phys.* 2004 May 1;59(1):146-51.
4. Oh JL, Dryden MJ, Woodward WA. Locoregional control of clinically diagnosed multifocal or multicentric breast cancer after neoadjuvant chemotherapy and locoregional therapy. *J Clin Oncol.* 2006 Nov 1;24(31):4971-5
5. Meijnen P, Bartelink H. Multifocal ductal carcinoma in situ of the breast: a contraindication for breast-conserving treatment? *J Clin Oncol.* 2007 Dec 10;25(35):5548-9.
6. Chen H, Wu K, Wang M, et al: Standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: A large population-based study in the Surveillance, Epidemiology, and End Results database  
18. *Breast.* 2017 Oct;35:48-54.

<b>Axillary Lymph Node Dissection (ALND) without Neoadjuvant Chemotherapy</b>			
	Oxford		
	LoE	GR	AGO
▪ <b>Endpoint: Survival (if patient receives adequate multimodal therapy)</b>	3	D	-
▪ <b>Endpoint: Staging</b>	3	A	-
▪ <b>Endpoint: Locoregional control</b>	2a	A	+/-
▪ <b>pN+ (histologically confirmed pre-surgery)</b>	2a	B	+
▪ <b>cN0 pN0 (i+) (sn)</b>	1b	A	--
▪ <b>cN0 pN1mi (sn)</b>	2b	B	--
▪ <b>cN0 pN1 (sn) (T1/2, &lt; 3 SN+*, BCS + RT + adequate systemic therapy)</b>	1b	A	-
▪ <b>cN0 pN1 (sn) and mastectomy (no chestwall radiotherapy)</b>	1b	B	+**
▪ <b>cN0 pN1 (sn) and mastectomy (T1/2, &lt; 3 SN+, chestwall radiotherapy)</b>	5	D	+/-**
▪ <b>ALND indicated, but not feasible</b>			
▪ <b>Radiotherapy according to AMAROS trial (validated for cN0 pN1sn)</b>	1b	B	+

\* ACOSOG 2011 trial protocol without clear definition of gross extra nodal disease  
 \*\* Study participation recommended



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Statement: Axillary lymph node dissection

1. Brackstone M, Baldassarre FG, Perera FE et al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol. 2021 Sep 20;39(27):3056-3082. doi: 10.1200/JCO.21.00934
2. Kuehn T, Bembenek A, Decker T. A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer. 2005 Feb 1;103(3):451-61
3. Rudenstam CM, Zahrieh D, Forbes JF: Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 24(3): 337-344, 2006.
4. Van la Parra: The value of sentinel lymph node biopsy in ductal carcinoma in situ (DCIS) and DCIS with microinvasion of the breast. Eur J Surg Oncol. 2008 Jun;34(6):631-5
5. Gerber B, Heintze K, Stubert J, et al. Axillary lymph node dissection in early-stage invasive breast cancer: is it still standard today? Breast Cancer Res Treat. 2011 Aug;128(3):613-24. Epub 2011 Apr 27. Review.
6. Lyman GH, Temin S, Edge SB, et al; American Society of Clinical Oncology Clinical Practice. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. Clin Oncol. 2014 May 1;32(13):1365-83

7. Lyman GH, Somerfield MR, Bosserman CD et al. Sentinel Lymph Node Biopsy for Patients with Early Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. DOI :10.1200/JCO.2016.71.
8. Bromham N, Schmidt-Hansen M, Astin M, et al. Axillary treatment for operable primary breast cancer. Cochrane Database Syst Rev. 2017 Jan 4;1:CD004561.

pN+ (pre-surgery) without neoadjuvant systemic therapy LoE 2a B AGO +

1. Euhus DM. Management of the clinically positive axilla. Breast J. 2020 Jan;26(1):35-38.

cN0 pN0(sn)(i+)LoE 1b A AGO –

1. Rutgers EJ. Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. J Clin Oncol. 2008 Feb 10;26(5):698-702.
2. Li Y, Zhang H, Zhang W, et al: A competing risk analysis model to determine the prognostic value of isolated tumor cells in axillary lymph nodes for T1N0M0 breast cancer patients based on the surveillance, epidemiology, and end results database. Frontiers in Oncology 10:572316, 2020

cN0 pN1 (mi) LoE 2b B AGO --

1. Mamtani A, Patil S, Stempel M, et al. Axillary Micrometastases and Isolated Tumor Cells Are Not an Indication for Post-mastectomy Radiotherapy in Stage 1 and 2 Breast Cancer. Ann Surg Oncol. 2017 Aug;24(8):2182-2188.
2. Cserni G, Gregori D, Merletti F: Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. Br J Surg 91(10): 1245-1252, 2004.
3. Rutgers EJ. Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. J Clin Oncol. 2008 Feb 10;26(5):698-702
4. Galimberti V, Cole BF, Zurrada S, et al. International Breast Cancer Study Group Trial 23-01 investigators. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013 Apr;14(4):297-305.



cN0 pN 1(sn) ( cT1/2 , < 3 SN +, BCS + tangential radiation field, adequate systemic therapy) LoE 1b A AGO -

1. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017 Sep 12;318(10):918-926.
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4. Poodt IGM, Spronk PER, Vugts G et al. Trends on Axillary Surgery in Nondistant Metastatic Breast Cancer Treated Between 2011 and 2015: A Dutch Population based Study in The ACOSOC Z0011 and AMAROS Era. Ann Surg Oncol 2018;26(6):1084-1090.
5. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. J Clin Oncol. 2014 Nov 10;32(32):3600-6.
6. Barrio AV, Downs-Canner S, Edelweiss M et al. Microscopic Extracapsular Extension in Sentinel Lymph Nodes Does Not Mandate Axillary Dissection in Z0011-Eligible Patients. Ann Surg Oncol. 2019 Dec 9.

cN0 pN1 (sn) and mastectomy (no chestwall radiotherapy) LoE 1b B AGO +\*

1. Cody HS 3rd. Extending ACOSOG Z0011 to Encompass Mastectomy: What Happens Without RT? Ann Surg Oncol. 2017 Mar;24(3):621-623.

ALND indicated, but not feasible – Radiotherapy according to AMAROS-trial (validated for cN0 pN1sn) LoE 1b B AGO +

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ACOSOG Z0011 gross extra nodal disease was not clearly defined in the protocol: A, Giuliano: personal email communication January 2023

Axillary Surgery and NACT							Oxford		
							LoE	GR	AGO
cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology			
cN0*	No surgery before NACT	ycN0	SLNE	++	ypN0 (sn)	none	2b	B	++
					ypN0 (i+) (sn)	ALND	2b	C	+/-
					ypN1mi (sn)	ALND	2b	C	+
					ypN1 (sn)	ALND	2b	C	++

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\* Study participation in EUBREAST-01 recommended

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Statement: SLNE after NACT

1. El Hage Chehade H, Headon H, El Tokhy O et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. *Am J Surg.* 2016 Nov;212(5):969-981.

Axillary Surgery and NACT (cN+)							Oxford		
							LoE	GR	AGO
cN status (before NACT)	pN status (before NACT)	ycN status (after NACT)	Axillary surgery (after NACT)	AGO	ypN status (after NACT and surgery)	Surgical consequence based on histopathology			
cN+*	pN+ <sub>CSB</sub>	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
				ypN0 (i+)	ALND	2b	B	+/-	
				ypN+ inkl. ypN1mi	ALND	2b	B	+	
			SLNE	+/-	ypN0	none	2b	B	+/-
				ypN0 (i+)	ALND	2b	B	+/-	
		ypN+ inkl. ypN1mi		ALND	2b	B	+		
		TLNE	+/-	ypN0	none	2b	B	+/-	
			ypN0 (i+)	ALND	3b	B	+/-		
			ypN+ inkl. ypN1mi	ALND	3b	B	+		
ycN+**	ALND	++	ypN0 / ypN+	none	2b	B	++		

\* Study participation in AXSANA recommended, \*\* Cave: In 30.3% false-positive findings, consider CNB if necessary



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Statement: SLNE after NACT

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Statement: False-positives in ALND after ycN+

1. Hartmann S, Kühn T, Hauptmann M et al., Axillary staging after neoadjuvant chemotherapy for initially node-positive breast carcinoma in Germany. Geburtsh Frauenheilk 2022, online

Statement: TLNE alone:

1. Swarnkar PK, Tayeh S, Michell MJ et al., The Evolving Role of Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) after Neoadjuvant Chemotherapy (NACT) for Node-Positive Breast Cancer: Systematic Review and Pooled Analysis. Cancers (Basel) 2021; 13(7):1539

<b>Targeted Axillary Dissection (TAD) = TLNE + SLNE</b>			
	Oxford		
	LoE	GR	AGO
▪ Core needle biopsy and marking of suspicious lymph nodes (LN)	2b	B	++
▪ Marking of multiple LN if more than one LN is suspicious	2b	B	+/-
▪ Evidence for comparison of different markers (clip / coil, carbon, magnetic seed, radar reflector, radiofrequency-based marker etc.) is insufficient *	2b	B	
▪ TAD in case of 1-3 suspicious LN before NACT	2b	B	+
▪ TAD in case of ≥ 4 suspicious LN before NACT	5	D	+/-
▪ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
▪ Immunohistochemistry for ITC detection	5	D	+/-
▪ ALND in case of pre- or intraoperatively undetectable marker	5	D	+
▪ Further intervention to retrieve lost marker (incl. after ALND)	5	D	-
▪ TLNE only without SLNE	2B	B	+/-

\* Study participation in AXSANA recommended



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Statement: TLNE alone:

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		<b>Sentinel Lymph Node Excision (SLNE) Indications I</b>		
		<b>Oxford</b>		
		<b>LoE</b>	<b>GR</b>	<b>AGO</b>
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1E</p> <p>In collaboration with:</p>  <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	▪ Clinically / sonographically negative axilla (cN0)	<b>1b</b>	<b>A</b>	<b>++</b>
	▪ cT 1–2	<b>2b</b>	<b>A</b>	<b>++</b>
	▪ omission of SLNE according to SOUND trial	<b>1b</b>	<b>B</b>	<b>+</b>
	▪ cT 3–4c	<b>3b</b>	<b>B</b>	<b>+</b>
	▪ Multifocal / multicentric breast cancer	<b>2b</b>	<b>B</b>	<b>+</b>
	▪ DCIS			
	▪ Mastectomy	<b>3b</b>	<b>B</b>	<b>+</b>
	▪ BCT	<b>3b</b>	<b>B</b>	<b>-</b>
	▪ DCIS in male	<b>5</b>	<b>D</b>	<b>+/-</b>
	▪ Male breast cancer	<b>2b</b>	<b>B</b>	<b>+</b>
▪ Omission of axillary intervention in elderly patients (≥ 70 yrs., co-morbidities, pT1, HR+)	<b>3b</b>	<b>B</b>	<b>+/-</b>	

### Statement: SLNE

1. Brackstone M, Baldassarre FG, Perera FE et al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol. 2021 Sep 20;39(27):3056-3082. doi: 10.1200/JCO.21.00934. Epub 2021 Jul 19.
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7. Rutgers EJ.Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. J Clin Oncol. 2008 Feb 10;26(5):698-702
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- experience of the European institute of oncology on 854 patients in 10 years. *Ann Surg.* 2008 Feb;247(2):315-9
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  10. Pugliese MS, Karam AK, Hsu M, et al. Predictors of Completion Axillary Lymph Node Dissection in Patients With Immunohistochemical Metastases to the Sentinel Lymph Node in Breast Cancer. *Ann Surg Oncol.* 2009 Dec 22. [Epub ahead of print]
  11. Lyman GH, Temin S, Edge S et al. American Society of Clinical Oncology Clinical Practice. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *Clin Oncol.* 2014 May 1;32(13):1365-83
  12. Lyman GH, Somerfield MR et al. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(5):561–564.
  13. Charalampoudis P, Markopoulos C, Kovacs T.: Controversies and recommendations regarding sentinel lymph node biopsy in primary breast cancer: A comprehensive review of current data. *Eur J Surg Oncol.* 2017 Nov 13. pii: S0748-7983(17)30955-1. doi: 10.1016/j.ejso.2017.10.215. [Epub ahead of print]
  14. Morrow M1, Van Zee KJ, Patil S, et al: Axillary Dissection and Nodal Irradiation Can Be Avoided for Most Node-positive Z0011-eligible Breast Cancers: A Prospective Validation Study of 793 Patients. *Ann Surg.* 2017 Sep;266(3):457-462.
  15. Gentilini, Botteri, Sangalli et al., Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial, *JAMA Oncol.* 2023 Nov 1;9(11):1557-1564

Statement: preoperative FNA / CNB (core needle biopsy) of suspicious lymph nodes

1. Houssami N, Ciatto S, Turner RM, et al. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer – a metaanalysis. *Ann Surg Oncol* 2011;254:243-251
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Statement: Multifocal / multicentric MaCa

1. Ferrari A, Dionigi P, Rovera F. Multifocality and multicentricity are not contraindications for sentinel lymph node biopsy in breast cancer surgery. *World J Surg Oncol*. 2006 Nov 20;4:79.

Statement: DCIS

1. Tuttle TM, Shamliyan T, Virnig BA, et al. The impact of sentinel lymph node biopsy and magnetic resonance imaging on important outcomes among patients with ductal carcinoma in situ. *J Natl Cancer Inst Monogr*. 2010;2010(41):117-20.
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Statement: Male

1. Boughhey JC et al. Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. *J Am Coll Surg* 2006 Oct;203(4):475-80.
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Statement: Elderly

1. Reimer T, Gerber B. Quality-of-life considerations in the treatment of early-stage breast cancer in the elderly. *Drugs Aging*. 2010 Oct 1;27(10):791-800.
2. Gerber B, Heintze K, Stubert J, et al. Axillary lymph node dissection in early-stage invasive breast cancer: is it still standard today? *Breast Cancer Res Treat*. 2011 Aug;128(3):613-24


Statement: Lymphedema

1. Miller CL, Specht MC, Skolny MN, et al. Sentinel lymph node biopsy at the time of mastectomy does not increase the risk of lymphedema: implications for prophylactic surgery. *Breast Cancer Res Treat*. 2012 Oct;135(3):781-9.






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Guidelines Breast  
Version 2024.1D

In Zusammen-  
arbeit mit:



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## Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes

### The SOUND Randomized Clinical Trial

Gentilini et al. JAMA Oncology, 2023

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- Prospective noninferiority phase 3 randomized clinical trial
- cT1a-c, preoperative negative axillary ultrasound = cN0 (ultrasound)
- 1463 patients included, 1405 intention-to-treat analysis, 708 SLNB, 697 no-SLNB
- Median age 60 years (52-68 years), median tumor size 1.1 cm (0,8-1.5 cm)
- Tumor biology: 87,8% HR+/HER2 neg.
- Results
  - Follow up 5.7 years (5.0-6.8 years), positive LN SLNB-group 13.7% ( $\geq 4$  LN 0.6%)
  - No statistical difference according to BCT, mastectomy, hormone therapy (97.9% vs. 98.9%) chemotherapy (20.1 vs. 17.5%), radiotherapy (98.0 vs. 97.6%)
  - **5 years DDFS 97.7% SLNB group vs. 98.0% in no-SLNB group ( $p = 0.67$ , HR 0.84, 90CI 0.45-1.54, noninferiority  $p = 0.02$ )**
  - Locoregional relapse 1.7% SLNB group vs. 1.6% in no-SLNB group
  - Axilla recurrence 1.7% SLNB group vs. 1.6% in no-SLNB group
  - Distant metastases 1.8% SLNB group vs. 2.0% in no-SLNB group
  - Deaths 3.0% SLNB group vs. 2.6% in no-SLNB group
- **CAVE: ultrasonography of axilla might be difficult, no details of radiotherapy presented, impact on systemic treatment decisions possible (e.g. CDK4/6 inhibitors), longer follow up needed**

1. Gentilini, Botteri, Sangalli et al., Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial, JAMA Oncol. 2023 Nov 1;9(11):1557-1564

<b>Sentinel Lymph Node Excision (SLNE) Indications II</b>			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>During pregnancy and / or breast feeding (only <sup>99m</sup>Tc-colloid, no patent or methylene blue dye, no data to SPIO or ICG)</b></li> </ul>	<b>3</b>	<b>C</b>	<b>++</b>
<ul style="list-style-type: none"> <li>▪ <b>After prior tumor excision</b></li> </ul>	<b>2b</b>	<b>B</b>	<b>+</b>
<ul style="list-style-type: none"> <li>▪ <b>After prior major breast surgery (e.g. reduction mammoplasty)</b></li> </ul>	<b>3b</b>	<b>C</b>	<b>+/-</b>
<ul style="list-style-type: none"> <li>▪ <b>Ipsilateral breast recurrence after prior BCS and prior SLNE</b></li> </ul>	<b>4</b>	<b>D</b>	<b>-</b>
<ul style="list-style-type: none"> <li>▪ <b>SLNE in the mammary internal chain</b></li> </ul>	<b>2b</b>	<b>B</b>	<b>-</b>
<ul style="list-style-type: none"> <li>▪ <b>After axillary surgery</b></li> </ul>	<b>3b</b>	<b>B</b>	<b>+/-</b>
<ul style="list-style-type: none"> <li>▪ <b>Prophylactic bilateral / contralateral mastectomy</b></li> </ul>	<b>3b</b>	<b>B</b>	<b>--</b>
<ul style="list-style-type: none"> <li>▪ <b>Inflammatory breast cancer</b></li> </ul>	<b>3b</b>	<b>C</b>	<b>-</b>



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Statement: pregnancy

1. Khera SY, Kiluk JV, Hasson DM Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. Breast J. 2008 May-Jun;14(3):250-4
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Statement: internal mammarian

1. Avisar E, Molina MA, Scarlata M: Internal mammary sentinel node biopsy for breast cancer. Am J Surg. 2008 Oct;196(4):490-4.
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3. Wouters MW, van Geel AN, Menke-Pluijmers M: Should internal mammary chain (IMC) sentinel node biopsy be performed? Outcome in 90 consecutive non-biopsied patients with a positive IMC scintigraphy. Breast. 2008 Apr;17(2):152-8.

Statement: prophylactic mastectomy

1. Dupont et al. The role of sentinel lymph node biopsy in women undergoing prophylactic mastectomy. Am J Surg 2000 Oct;180(4):274-7
2. Soran A et al.: Is routine sentinel lymph node biopsy indicated in women undergoing contralateral prophylactic mastectomy? Magee-Womens Hospital experience. Ann Surg Oncol 2007 Feb;14(2):646-51.
3. Boughey JC et al.: Decision analysis to assess the efficacy of routine sentinel lymphadenectomy in patients undergoing prophylactic mastectomy. Cancer 2007 Dec 1;110(11):2542-50

Statement: After previous tumor excision

1. Celebioglu et al.: Sentinel node biopsy in non-palpable breast cancer and in patients with a previous diagnostic excision. Eur J Surg Oncol 2007 Apr;33(3):276-80.

Statement: previous major breast surgery

1. Intra et al. Sentinel lymph node biopsy is feasible even after total mastectomy. J Surg Oncol 2007 Feb 1;95(2):175-9
2. Kaminski A, Amr D, Kimbrell ML: Lymphatic mapping in patients with breast cancer and previous augmentation mammoplasty. Am Surg. 2007 Oct;73(10):981-3
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Statement: Ipsilateral breast recurrence after prior BCS and prior SLNB



1. Mattia Intra M, Triro G, Viale G: Second Biopsy of Axillary Sentinel Lymph Node for Reappearing Breast Cancer After Previous Sentinel Lymph Node Biopsy. *Ann Surg Oncol.* 2005;12(11):895-9
2. Intra et al. Second axillary sentinel node biopsy for ipsilateral breast tumour recurrence. *Br J Surg* 2007 Oct;94(10):1216-9
3. Schrenk P et al. Lymphatic mapping in patients with primary or recurrent breast cancer following previous axillary surgery. *Eur J Surg Oncol.* 2008 Aug;34(8):851-6.
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5. Intra M, Viale G, Vila J, et al. Second Axillary Sentinel Lymph Node Biopsy for Breast Tumor Recurrence: Experience of the European Institute of Oncology. *Ann Surg Oncol.* 2015 Jul;22(7):2372-7.
6. Moffat FL Jr, Yakoub D.: Bilateral mastectomy and the retreat from breast-conserving surgery. *Breast Cancer Res Treat.* 2016 Aug;159(1):15-30.
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Statement: inflammatory breast cancer

1. Fayanju OM, Ren Y, Greenup RA, et al. Extent of axillary surgery in inflammatory breast cancer: a survival analysis of 3500. *Breast Cancer Res Treat.* 2020 Feb;180(1):207-217.
2. Singletary SE. Surgical management of inflammatory breast cancer. *Semin Oncol.* 2008 Feb;35(1):72-7
3. van Uden DJ, van Laarhoven HW, Westenberg AH, et al. Inflammatory breast cancer: An overview. *Crit Rev Oncol Hematol.* 2015 Feb;93(2):116-26.
4. Matro JM, Li T, Cristofanilli M, Hughes ME, et al. Inflammatory breast cancer management in the national comprehensive cancer network: the disease, recurrence pattern, and outcome. *Clin Breast Cancer.* 2015 Feb;15(1):1-7.

Statement: Others

1. Schwartz GF, Giuliano AE, Veronesi U; Consensus Conference Committee. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. *Cancer* 2002;94:2542-51
2. Kuehn T, Bembenek A, Decker T. A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. *Cancer*. 2005 Feb 1;103(3):451-61
3. Golshan M et al. Sentinel lymph node biopsy for occult breast cancer detected during breast reduction surgery. *Am Surg* 2006 May;72(5):397-400
4. Schrenk et al. Symmetrization reduction mammoplasty combined with sentinel node biopsy in patients operated for contralateral breast cancer. *J Surg Oncol* 2006 Jul 1;94(1):9-15.
5. Lyman GH, Temin S, Edge SB, et al. American Society of Clinical Oncology Clinical Practice. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *Clin Oncol*. 2014 May 1;32(13):1365-83.
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		Oxford		
		LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2024.1E</p> <p>In collaboration with:</p>  <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	<ul style="list-style-type: none"> <li>▪ <b><sup>99m</sup>Tc Kolloid</b></li> <li>▪ <b>Preoperative lymphoscintigraphy (added information limited, but mandatory by legal regulations)*</b></li> <li>▪ <b>Patent blue dye</b></li> <li>▪ <b>Indocyanin green (ICG)<sup>°</sup></b></li> <li>▪ <b>SPIO<sup>#</sup></b></li> <li>▪ <b>Methylene blue</b></li> </ul>			
		<b>1a</b>	<b>A</b>	<b>++</b>
		<b>1b</b>	<b>A</b>	<b>+</b>
		<b>1a</b>	<b>A</b>	<b>+/-</b>
		<b>2a</b>	<b>B</b>	<b>+</b>
		<b>2a</b>	<b>B</b>	<b>+</b>
	<b>2a</b>	<b>B</b>	<b>+/-</b>	
<p>* In Germany required for quality assurance of nuclear medicine</p> <p># SPIO: Superparamagnetic Iron Oxide (Caveat: impaired MRI-sensitivity during follow-up)</p> <p>° no approval for LN marking in the axilla, off-label</p>				

### Statement radiotracer/blue dye:

1. Shams S, Lippold K, Blohmer JU, et al. A Pilot Study Evaluating the Effects of Magtrace<sup>®</sup> for Sentinel Node Biopsy in Breast Cancer Patients Regarding Care Process Optimization, Reimbursement, Surgical Time, and Patient Comfort Compared With Standard Technetium99. *Ann Surg Oncol.* 2021 Jun;28(6):3232-3240. doi: 10.1245/s10434-020-09280
2. Lyman GH, Somerfield MR et al. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(5):561–564.
3. Ditsch N, Rubio IT, Gasparri ML, et al. Breast and axillary surgery in malignant breast disease: a review focused on literature of 2018 and 2019. *Curr Opin Obstet Gynecol.* 2020;32(1):91–99.
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5. Rodier JF, Velten M, Wilt M, et al. Prospective multicentric randomized study comparing periareolar and peritumoral injection of radiotracer and blue dye for the detection of sentinel lymph node in breast sparing procedures: FRANSENODE trial. *J Clin Oncol.* 2007 Aug 20;25(24):3664-

6. Bines S, Kopkash K, Ali A, Fogg L, et al. The use of radioisotope combined with isosulfan Blue dye is not superior to radioisotope alone for the identification of sentinel lymph nodes in patients with breast cancer. *Surgery*. 2008 Oct;144(4):606-9; discussion 609-10.
7. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol*. 2010 Jul;17(7):1854-61.
8. Pesek S, Ashikaga T, Krag LE, et al. The false-negative rate of sentinel node biopsy in patients with breast cancer: a meta-analysis. *World J Surg* 2012;36(9): 2239-2251
9. Lyman GH, Temin S, Edge SB, et al. American Society of Clinical Oncology Clinical Practice\_ Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *Clin Oncol*. 2014 May 1;32(13):1365-83
10. Ang CH, Tan MY, Teo C, et al. Blue dye is sufficient for sentinel lymph node biopsy in breast cancer. *Br J Surg*. 2014 Mar;101(4):383-9; discussion 389.
11. Ahmed M, Purushotham AD, Horgan K, et al. Meta-analysis of superficial versus deep injection of radioactive tracer and blue dye for lymphatic mapping and detection of sentinel lymph nodes in breast cancer. *Br J Surg*. 2015 Feb;102(3):169-81.
12. Liu HJ, Sun MS, Liu LY et al. The detection rate of methylene blue combined with another tracer in sentinel lymph node biopsy of early-stage breast cancer: a systematic review and network meta-analysis. *Transl Cancer Res*. 2021 Dec;10(12):5222-5237.

#### Statement Magnetic Tracer

1. Shams S, Lippold K, Blohmer JU, et al. A Pilot Study Evaluating the Effects of Magtrace® for Sentinel Node Biopsy in Breast Cancer Patients Regarding Care Process Optimization, Reimbursement, Surgical Time, and Patient Comfort Compared With Standard Technetium99. *Ann Surg Oncol*. 2021 Jun;28(6):3232-3240. doi: 10.1245/s10434-020-09280
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Statement: pre-operative lymphoscintigraphy

1. Kummel S, Holtschmidt J, Gerber B et al. Randomized surgical multicenter trial to evaluate the usefulness of lymphoscintigraphy (LSG) prior to sentinel node biopsy (SLNB) in early breast cancer: SenSzi (GBG80) trial. Journal of Clinical Oncology 35, no. 15\_suppl (May 2017) 555-555.

Statement: methylene blue

1. Varghese P, Mostafa A, Abdel-Rahman AT, et al. Methylene blue dye versus combined dye-radioactive tracer technique for sentinel lymph node localisation in early breast cancer. Eur J Surg Oncol. 2007 Mar;33(2):147-52.
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8. Yang S, Xiang HY, Xin L et al. Retrospective analysis of sentinel lymph node biopsy using methylene blue dye for early breast cancer. Chin Med J (Engl). 2021 Jan 11;134(3):318-325

Statement: Methylene blue / patent blue and anaphylactic reactions:

1. Perenyi M, Barber ZE, Gibson J et al. Anaphylactic Reaction Rates to Blue Dyes Used for Sentinel Lymph Node Mapping:



Systematic Review and Meta-analysis. *Ann Surg.* 2021 Jun 1;273(6):1087-1093.

2. Liberale V, Tripodi E, Ottino L, Biglia N. Surgery on breast cancer in pregnancy. *Transl Cancer Res.* 2019 Oct;8(Suppl 5):S493-S502.

#### Statement: ICG

1. Mok CW, Tan SM, Zheng Q, Shi L. Network meta-analysis of novel and conventional sentinel lymph node biopsy techniques in breast cancer. *BJS Open.* 2019 Mar 25;3(4):445-452.
2. Sugie T, Ikeda T, Kawaguchi A, et al. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: a meta-analysis. *Int J Clin Oncol.* 2017 Feb;22(1):11-17.
3. Zhang X, Li Y, Zhou Y, et al. Diagnostic Performance of Indocyanine Green-Guided Sentinel Lymph Node Biopsy in Breast Cancer: A Meta-Analysis. *PLoS One.* 2016 Jun 9;11(6):e0155597.
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6. Kedrzycki MS, Leiloglou M, Ashrafian H et al. Meta-analysis Comparing Fluorescence Imaging with Radioisotope and Blue Dye-Guided Sentinel Node Identification for Breast Cancer Surgery. *Ann Surg Oncol.* 2021 Jul;28(7):3738-3748.

#### Statement: SPIO

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## Surgical Approach in the Neoadjuvant Setting

	Oxford		
	LoE	GR	AGO
▪ <b>Early marking of tumor (incl. detailed topographic documentation)</b>	5	D	++
▪ <b>Surgical removal of tumor / representative excision of post-therapeutic, marked tumor area</b>	2b	C	++
▪ <b>Tumor resection in new margins</b>	2b	C	++
▪ <b>Microscopically clear margins</b>	2a	B	++

**For „Surgery after neoadjuvant chemotherapy“ see chapter „Neoadjuvant chemotherapy“**

Statement: clip marking

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Statement: tumor free margins ...


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## Begin of Adjuvant Therapy after Primary Surgery

	Oxford		
	LoE	GR	AGO
▪ <b>Start adjuvant systemic therapy and radiotherapy (RT) as soon as possible (asap) after surgery</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>Start of adjuvant chemotherapy +/- HER2 therapy asap after surgery, prior to RT</b>	<b>1b</b>	<b>A</b>	<b>++</b>
▪ <b>Without cytotoxic therapy +/- anti-HER2 therapy:</b>			
▪ Start adjuvant RT within 6–8 weeks after surgery	<b>2b</b>	<b>B</b>	<b>++</b>
▪ Start endocrine therapy after surgery asap	<b>5</b>	<b>D</b>	<b>++</b>
▪ Endocrine therapy concurrent with RT	<b>2b</b>	<b>B</b>	<b>+</b>

### Statement: Timing of radiation and chemotherapy

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#### Statement AI concurrent with radiotherapy

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