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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 2002–2021:

Bauerfeind / Blohmer / Böhme / Brunnert / Costa / Ditsch / Fallenberg /
Fersis / Friedrich / Gerber / Hanf / Janni / Junkermann / Kaufmann /
Kühn / Kümmel / Möbus / Nitz / Rezai / Simon / Solomayer / Thomssen /
Thill / Thomssen / Untch / Wöckel

■ Version 2022:


Banys-Paluchowski / Gerber



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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

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.

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

Pre-therapeutic Assessment of Breast and Axilla			
	Oxford		
	LoE	GR	AGO
■ Clinical examination	5	D	++
■ Mammography	2b	B	++
■ + Tomosynthesis (DBT)***	2b	B	+
■ Contrast-enhanced mammography (alone or as adjunct)	2a	B	+
■ Sonography (breast and axilla)	2a	B	++
■ MRI*	1b	B	+
■ Minimally invasive biopsy** (CNB, VAB)	1b	A	++
■ Axilla CNB, if lymph node is suspect	2b	B	++
■ Breast-CT	5	D	-
■ Axillary PET / CT	2b	B	-

* MRI-guided vacuum biopsy is mandatory in case of MRI-detected additional lesions (in house or with cooperations). Individual decision for patients at high familiar risk, with dense breast (density C/D), lobular invasive tumors, suspicion of multilocular disease. No reduction in re-excision rate.
 ** Histopathology of additional lesions if relevant for treatment
 *** Replacement of 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.

US-Axilla +FNA/CNB

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.
4. 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.
3. Debald M, Abramian A, Nemes L, et al. Who may benefit from preoperative MRI? A single-center analysis of 1102 consecutive patients with primary breast cancer. Breast Cancer Res Treat 2015;153(3):531-537
4. Arnaut A, Catley C, Booth CM, et al. Use of preoperative Magnetic Resonance Imaging for breast cancer: A Canadian population-based study. JAMA Oncol 2015;1(9):1238-1250
5. Fancellu A, Turner RM, Dixon JM, et al. Metaanalysis of the effect of preoperative MRI on the surgical management of ductal carcinoma in situ. Brit J Surg2015;192(8)883-893
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
10. Riedl CC, Luft N, Clemens B, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasonography regardless of patient mutation status, age and breast density. JCO 2015;33(10):1128-1135
 11. El Sharouni M, Postma EL, Menezes GLG et al. High prevalence of MRI-detected contralateral and ipsilateral malignant findings in patients with invasive ductolobular breast cancer: Impact on surgical management. Clin Breast Cancer. 2016 Aug;16(4):269-75.
 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.
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 14. Lobbes MB, Vriens IJ, van Bommel AC, et al. Breast MRI increases the number of mastectomies for ductal cancers, but decreases them for lobular cancers. Breast Cancer Res Treat. 2017;162:353-364.
 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
 16. Achim Wöckel, Jasmin Festl, Tanja Stüber, et al: Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. Geburtshilfe Frauenheilkd. 2018 Oct; 78(10): 927–948.

Reviews CESM:

1. Dromain, C., N. Viesti-Violi, and J.Y. Meuwly, Angiomammography: A review of current evidences. Diagn Interv Imaging, 2019.
2. Patel, B.K., M.B.I. Lobbes, and J. Lewin, Contrast Enhanced Spectral Mammography: A Review. Semin Ultrasound CT MR, 2018. 39(1): p. 70-79.
3. Tagliafico, A.S., et al., Diagnostic performance of contrast-enhanced spectral mammography: Systematic review and meta-analysis. Breast, 2016. 28: p. 13-9.
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.
5. Sogani J, Mango VL, Keating D, et al. Contrast-enhanced mammography: past, present, and future. Clin Imaging. 2021;69:269-79.

CESM Originalarbeiten:

1. Luczynska, E., et al., Comparison of the Mammography, Contrast-Enhanced Spectral Mammography and Ultrasonography in a Group of 116 patients. *Anticancer Res*, 2016. 36(8): p. 4359-66.
2. Fallenberg, E.M., et al., Contrast-enhanced spectral mammography: Does mammography provide additional clinical benefits or can some radiation exposure be avoided? *Breast Cancer Res Treat*, 2014. 146(2): p. 371-81.
3. Tennant, S.L., et al., Contrast-enhanced spectral mammography improves diagnostic accuracy in the symptomatic setting. *Clin Radiol*, 2016. 71(11): p. 1148-55.
4. Fallenberg, E.M., et al., Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation. *Eur Radiol*, 2017. 27(7): p. 2752-2764.
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.
6. Kim, E.Y., et al., Diagnostic Value of Contrast-Enhanced Digital Mammography versus Contrast-Enhanced Magnetic Resonance Imaging for the Preoperative Evaluation of Breast Cancer. *Journal of breast cancer*, 2018. 21(4): p. 453-462.
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8. Gluskin J, Rossi Saccarelli C, Avendano D, et al. Contrast-Enhanced Mammography for Screening Women after Breast Conserving Surgery. *Cancers (Basel)*. 2020;12(12).
9. Sogani J, Mango VL, Keating D, et al. Contrast-enhanced mammography: past, present, and future. *Clin Imaging*. 2021;69:269-79.
10. González-Huebra I, Malmierca P, Elizalde A, et al. The accuracy of titanium contrast-enhanced mammography: a retrospective multicentric study. *Acta Radiol*. 2020;61(10):1335-42.
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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. 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.

15. Pretherapeutic Imaging for Axillary Staging in Breast Cancer: A Systematic Review and Meta-Analysis of Ultrasound, MRI and FDG PET. Le Boulc'h M, Gilhodes J, Steinmeyer Z, et al. Clin Med. 2021 Apr 6;10(7):1543. doi: 10.3390/jcm10071543.PMID: 33917590 Free PMC article. Review.

Pre-therapeutic Staging			
	Oxford		
	LoE	GR	AGO
	5	D	++
History and clinical examination Only in case of high metastatic potential and / or symptoms and / or indication for (neo-) adjuvant chemotherapy and / or antibody-therapy:			
CT scan of thorax / abdomen	2a	B	+
Bone scan	2b	B	+
Chest X-ray	5	C	+/-
Liver ultrasound	5	D	+/-
Further investigation in case of suspicious lesions (e.g. liver-MRI, CEUS*, biopsy etc.)	2a	B	+
FDG-PET or FDG-PET / CT**	2b	B	+/-
Whole body MRI	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
2. Gerber B, Seitz E, Muller H et al: Perioperative screening for metastatic disease is not indicated in patients with primary breast cancer and no clinical signs of tumor spread. Breast Cancer Res Treat 82:29-37; 2003
3. Schneider C, Fehr MK, Steiner RA et al: Frequency and distribution pattern of distant metastases in breast cancer patients at the time of primary presentation Arch Gynecol Obstet. 2003 Nov;269(1):9-12.
4. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDGPET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat 2005;90(2):105–12.
5. Schmidt GP, Baur-Melnyk A, Haug A, et al.: Comprehensive imaging of tumor recurrence in breast cancer patients using whole-body MRI at 1.5 and 3 T compared to FDG–PET–CT. European Journal of Radiology 2008; 65, 47–58.
6. Shie P, Cardarelli R, Brandon D et al: Meta-analysis: comparison of F-18 Fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med. 2008 Feb;33(2):97-101.
7. Barrett T, Bowden DJ, Greenberg DC et al.: Radiological staging in breast cancer: which asymptomatic patients to image and how. British Journal of Cancer 2009; 101, 1522 – 1528.
8. Rong J, Wang S, Ding Q, et al. Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. Surg Oncol. 2013 Jun;22(2):86-91
9. Hong S, Li J, Wang S. 18FDG PET-CT for diagnosis of distant metastases in breast cancer patients. A meta-analysis. Surg Oncol. 2013 Jun;22(2):139-43.
10. Gutzeit A, Doert A, Froehlich JM, et al. Comparison of diffusion-weighted whole body MRI and skeletal scintigraphy for the detection of bone metastases in patients with prostate or breast carcinoma. Skeletal Radiol. 2010 Apr;39(4):333-43.

11. Department of Health. Diagnosis, staging and treatment of patients with breast cancer. National Clinical Guideline No. 7. June 2015. ISSN 2009-6259
12. Bychkovsky BL, Lin NU: Imaging in the evaluation and follow-up of early and advanced breast cancer: When, why, and how often? 2017; 31, 318–324.
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14. NCCN 2019: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. NCCN Evidence Blocks™. Version 3.2019 – September 6, 2019. https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf. Download Jan 19, 2020.
15. Mishima M, Toh U, Iwakuma N, et al. Evaluation of contrast Sonazoid-enhanced ultrasonography for the detection of hepatic metastases in breast cancer. Breast Cancer. 2016 Mar;23(2):231-41
16. Zhang L, Zhang L, Wang H, et al. Diagnostic performance of contrast-enhanced ultrasound and magnetic resonance imaging for detecting colorectal liver metastases: A systematic review and meta-analysis. Dig Liver Dis. 2019 Sep;51(9):1241-1248.
17. Ulaner GA, Castillo R, Goldman DA, et al. ¹⁸F-FDG-PET/CT for systemic staging of newly diagnosed triple-negative breast cancer. Eur J Nucl Med Mol Imaging 2016; 43:1937–1944
18. Ulaner GA, Castillo R, Wills J, et al. ¹⁸F-FDG-PET/CT for systemic staging of patients with newly diagnosed ER-positive and HER2-positive breast cancer. Eur J Nucl Med Mol Imaging 2017
19. Groheux D, Giacchetti S, Espié M, et al. The yield of ¹⁸F-FDG PET/CT in patients with clinical stage IIA, IIB, or IIIA breast cancer: a prospective study. J Nucl Med 2011; 52:1526–1534
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21. Ulaner GA. PET/CT for Patients With Breast Cancer: Where Is the Clinical Impact? AJR American journal of roentgenology. 2019;213(2):254-65.
22. Reddy Akepati NK, Abubakar ZA, Bikkina P.. Role of 18F-Fluorodeoxyglucose Positron-Emission Tomography/Computed Tomography Scan in Primary Staging of Breast Cancer Compared to Conventional Staging.. Indian J Nucl Med.; 2018.
23. Krammer J, Schnitzer A, Kaiser CG, et al. (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?. Eur Radiol. ; 2015.
24. Ng SP, David S, Alamgeer M, Ganju V.. Impact of Pretreatment Combined (18)F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging on Radiation Therapy Treatment Decisions in Locally Advanced Breast Cancer.. Int J Radiat Oncol Biol Phys.; 2015.
25. Goorts, B., Vöö, S., van Nijnatten, T.J.A. et al. Hybrid ¹⁸F–FDG PET/MRI might improve locoregional staging of breast cancer patients

prior to neoadjuvant chemotherapy. Eur J Nucl Med Mol Imaging 44, 1796–1805 (2017). <https://doi.org/10.1007/s00259-017-3745-x>


26. <https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/staging-breast-cancer>



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Evidence of Surgical Procedure

	Oxford LoE	GR
▪ Survival rates after lumpectomy + RT are at least equivalent to those after (modified) radical mastectomy	1a	A
▪ Local recurrence rates after skin sparing mastectomy are equivalent to those after mastectomy	2b	B
▪ Conservation of the NAC (nipple areola complex) is an adequate surgical procedure, if R0 resection is achieved	2b	C

Statement: lumpectomy – mastectomy

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer (2002) N Engl J Med 347:1233-1241
2. Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. NEJM 2002 Oct 17;347(16):1227-32
3. Christiansen P, Carstensen SL, Ejlersen B, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta Oncol. 2017 Nov 23:1-7.
4. de Boniface J, Szulkin R, Johansson ALV. Survival After Breast Conservation vs Mastectomy Adjusted for Comorbidity and Socioeconomic Status: A Swedish National 6-Year Follow-up of 48 986 Women. JAMA Surg 2021;156(7):628-637. doi: 10.1001/jamasurg.2021.1438
5. Van Maare MC, de Munck L, de Bock GH et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol. 2016;17(8):1158-1170. doi: 10.1016/S1470-2045(16)30067-5
6. Hofvind S, Holen A, Aas T et al. Women treated with breast conserving surgery do better than those with mastectomy independent of detection mode, prognostic and predictive tumor characteristics. Eur J Surg Oncol. 2015;41(10):1417-22. doi: 10.1016/j.ejso.2015.07.002.

7. Agarwal S, Pappas L, Neumayer L et al. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. JAMA Surg. 2014; 149(3):267-74. doi: 10.1001/jamasurg.2013.3049.

Statement: skin sparing mastectomy

1. Carlson GW, Bostwick J, Styblo TM et al. Skin-sparing mastectomy. Oncologic and reconstructive considerations. Ann Surg 1997; 225:570-575.
2. Kroll SS, Schusterman MA, Tadjalli HE et al. Risk of recurrence after treatment of early breast cancer with skin- sparing mastectomy Ann Surg Oncol 1997; 4:193-197.
3. Slavin SA, Schnitt SJ, Duda RB et al. Skin-sparing mastectomy and immediate reconstruction: oncologic risks and aesthetic results in patients with early-stage breast cancer. Plast Reconstr Surg 1998; 102:49-62.
4. Simmons RM, Fish SK, Gayle L et al. Local and distant recurrence rates in skin-sparing mastectomies compared with non-skin-sparing mastectomies. Ann Surg Oncol 1999; 6:676-681.
5. Rivadeneira D, Simmons RM, Fish SK et al. Skin-sparing mastectomy with immediate breast reconstruction: a critical analysis of local recurrence. Cancer 2000; 6:331-335.
6. Foster et al. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. Ann Surg Oncol 2002 Jun;9(5):462-6
7. Greenway RM, Schlossberg L, Dooley WC. Fifteen-year series of skin-sparing mastectomy for stage 0 to 2 breast cancer. Am J Surg 2005; 190:918-922.
8. Howard MA, Polo K, Pusic AL et al. Breast cancer local recurrence after mastectomy and TRAM flap reconstruction: incidence and treatment options. Plast Reconstr Surg 2006; 117:1381-1386.
9. Patani N, Devalia H, Anderson A et al. Oncological safety and patient satisfaction with skin-sparing mastectomy and immediate breast reconstruction. Surg Oncol 2007; 17:97-105.
10. Paepke S, Schmid R, Fleckner S, et al. Subcutaneous mastectomy with conservation of the nipple-areola skin: broadening the indications Ann Surg. 2009;250(2):288-92
11. Gerber et al.: Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. Ann Surg 2009 Mar;249(3):461-8
12. Lanitis S1, Tekkis PP, Sgourakis G, et al.: Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. Ann Surg. 2010 Apr;251(4):632-9.

Statement: Nipple sparing mastectomy

1. Petit JY, Veronesi U, Orecchia R et al. Nipple-sparing mastectomy in association with intra operative radiotherapy (ELIOT): A new type of mastectomy for breast cancer treatment. *Breast Cancer Res Treat* 2006; 96:47-51.
2. Sacchini V, Pinotti JA, Barros AC et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg* 2006; 203:704-714.
3. Caruso F, Ferrara M, Castiglione G et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. *Eur J Surg Oncol* 2006; 32:937-940.
4. Howard MA, Polo K, Pusic AL et al. Breast cancer local recurrence after mastectomy and TRAM flap reconstruction: incidence and treatment options. *Plast Reconstr Surg* 2006; 117:1381-1386
5. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: A prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol* 2008; 34:143-148.
6. Gerber et al.: Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg* 2009 Mar;249(3):461-8
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8. Burdge EC, Yuen J, Hardee M, et al. Nipple skin-sparing mastectomy is feasible for advanced disease. *Ann Surg Oncol*. 2013 Oct;20(10):3294-302.
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Breast-Conserving Surgery (BCS): Non-Palpable Lesions			
	Oxford		
	LoE	GR	AGO
■ Wire-guided localization	1a	A	++
■ Wireless intraoperative ultrasound-guided localization*	1a	A	++
■ Other procedures:**			
Radar reflectors	2b	B	+/-
Magnetic Seeds***	2b	B	+/-
Radiofrequency-based markers (RFID)	2b	B	+/-
Radionuclide-guided localization (ROLL)	1a	A	+/-
Radioactive seeds****	1a	A	+/-

* 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.
 ** according to approval
 *** not suitable for MRI-based response assessment under NACT
 **** not approved in Germany

Meta-analyses of different techniques:

1. Athanasiou 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.
2. Chan BKY, Wiseberg-Firtell JA, Jois RHS et al. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev. 2015 Dec 31;(12):CD009206. doi: 10.1002/14651858.CD009206.pub2

Meta-analysis intraoperative ultrasound vs. wire-guided localization:

1. Ahmed M, Douek M. Intra-operative ultrasound versus wire-guided localization in the surgical management of non-palpable breast cancers: systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Aug;140(3):435-46.
2. Pan H, Wu N, Ding H, et al. (2013) Intraoperative ultrasound guidance is associated with clear lumpectomy margins for breast cancer: a systematic review and meta-analysis. PLoS One 8:e74028. 10.1371/journal.pone.0074028
3. Banys-Paluchowski M, Rubio IT, Karadeniz Cakmak G et al. Intraoperative ultrasound-guided excision of non-palpable and palpable breast cancer: systematic review and meta-analysis. in press 2022

RCTs intraoperative ultrasound vs. wire-guided localization:

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: cohort studies:

1. Layeequr Rahman R, Puckett Y, et al. (2020) A decade of intraoperative ultrasound guided breast conservation for margin negative resection - Radioactive, and magnetic, and Infrared Oh My. Am J Surg 220:1410-1416. 10.1016/j.amjsurg.2020.09.008
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3. Ramos M, Diaz JC, Ramos T, et al. (2013) Ultrasound-guided excision combined with intraoperative assessment of gross macroscopic margins decreases the rate of reoperations for non-palpable invasive breast cancer. Breast 22:520-524. 10.1016/j.breast.2012.10.006
4. Arentz C, Baxter K, Boneti C, et al. (2010) Ten-year experience with hematoma-directed ultrasound-guided (HUG) breast lumpectomy. Ann Surg Oncol 17 Suppl 3:378-383. 10.1245/s10434-010-1230-x
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6. Yu CC, Chiang KC, Kuo WL, et al. (2013) Low re-excision rate for positive margins in patients treated with ultrasound-guided breast-conserving surgery. Breast 22:698-702. 10.1016/j.breast.2012.12.019
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- re-excisions and mastectomy rates in breast cancer. *Breast* 33:23-28. 10.1016/j.breast.2017.02.014
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11. Eggemann H, Costa SD, Ignatov A (2016) Ultrasound-Guided Versus Wire-Guided Breast-Conserving Surgery for Nonpalpable Breast Cancer. *Clin Breast Cancer* 16:e1-6. 10.1016/j.clbc.2015.09.001

Magnetic seeds: RCT:

1. Struik GM, Schermers B, Mares I et al. Randomized controlled trial comparing magnetic marker localization (MaMaLoc) with wire-guided localization in the treatment of early-stage breast cancer. *Breast J.* 2021;27(8):638-650. doi: 10.1111/tbj.14262.

Magnetic seeds: cohort studies:

1. Gera R, Tayeh S, et al: Evolving Role of Magseed in wireless localization of breast lesions: systematic review and pooled analysis of 1.559 procedures. *Anticancer Res* 40: 1809-1815, 2020
2. Murphy E, Quinn E, Stokes M et al. Initial experience of magnetic seed localization for impalpable breast lesion excision: First 100 cases performed in a single Irish tertiary referral centre. *Surgeon.* 2021 Apr 8:S1479-666X(21)00060-3. doi: 10.1016/j.surge.2021.02.010.
3. Powell M, Gate T, Kalake O et al. Magnetic Seed Localization (Magseed) for excision of impalpable breast lesions-The North Wales experience. *Breast J.* 2021 Jun;27(6):529-536. doi: 10.1111/tbj.14232. Epub 2021 Apr 15.
4. Kühn F, Simon CEE, Aliyeva I et al. A German Study Comparing Standard Wire Localization With Magnetic Seed Localization of Non-palpable Breast Lesions. *In Vivo.* May-Jun 2020;34(3):1159-1164. doi: 10.21873/invivo.11888.
5. Singh P, Scoggins ME, Sahin AA et al. Effectiveness and Safety of Magseed-localization for Excision of Breast Lesions: A Prospective, Phase IV Trial. *Ann Surg Open.* 2020 Dec;1(2):e008. doi: 10.1097/as9.0000000000000008.

Radar reflector markers: cohort studies (no RCTs available):

1. Kasem I, Mokbel K. Savi Scout® Radar Localisation of Non-palpable Breast Lesions: Systematic Review and Pooled Analysis of 842 Cases. *Anticancer Res.* 2020 Jul;40(7):3633-3643. doi: 10.21873/anticancer.14352.
2. Tingen JS, McKinley BP, Rinkliff JM et al. Savi Scout Radar Localization Versus Wire Localization for Breast Biopsy Regarding Positive

Margin, Complication, and Reoperation Rates. Am Surg. 2020 Aug;86(8):1029-1031. doi: 10.1177/0003134820939903. Epub 2020 Jul 28.

3. Wazir U, Kasem I, Michell MJ et al. Reflector-Guided Localisation of Non-Palpable Breast Lesions: A Prospective Evaluation of the SAVI SCOUT[®] System. Cancers (Basel). 2021 May 17;13(10):2409. doi: 10.3390/cancers13102409.
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Radiofrequency-based markers (RFID): cohort studies (no RCTs available):

1. Tayeh S, Wazir U, Mokbel K. The Evolving Role of Radiofrequency Guided Localisation in Breast Surgery: A Systematic Review. Cancers (Basel). 2021 Oct 5;13(19):4996. doi: 10.3390/cancers13194996.
2. McGugin C, Spivey T, Coopey S et al. Radiofrequency identification tag localization is comparable to wire localization for non-palpable breast lesions. Breast Cancer Res Treat. 2019 Oct;177(3):735-739. doi: 10.1007/s10549-019-05355-0.

Radioactive seeds (for RCTs see meta-analyses above):

1. Schermers B, van Riet YE, Schipper RJ et al. Nationwide registry study on trends in localization techniques and reoperation rates in non-palpable ductal carcinoma in situ and invasive breast cancer. Br J Surg. 2021 Oct 13;znab339. doi: 10.1093/bjs/znab339.

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.

Breast-Conserving Surgery (BCS): Resection Margins			
	Oxford		
	LoE	GR	AGO
Invasive breast cancer without extensive intraductal component (EIC)*			
<ul style="list-style-type: none"> Aim: tumor-free margins ("no ink on tumor" is sufficient even in case of unfavorable tumor biology) 	2a	A	++
<ul style="list-style-type: none"> Re-excision for invasive or non-invasive tumor cells reaching margin (final histology) 	2a	B	++
Invasive breast cancer with EIC*			
<ul style="list-style-type: none"> Re-excision for invasive or non-invasive tumor cells reaching margin (final histology) 	2a	B	++
<ul style="list-style-type: none"> Re-excision in case of a close margin of the intraductal component (< 2 mm on final histology)** 	2a	B	-
<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.
2. Houssami N, Macaskill P, Marinovich ML, Morrow M. 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 March ; 21(3): 717–730. doi:10.1245/s10434-014-3480-5
3. Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol. 2014 May 10;32(14):1502-6.
4. Consensus Guideline on Breast Cancer Lumpectomy Margins. The American Society of Breast Surgeons 2018. <https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Breast-Cancer-Lumpectomy-Margins.pdf>
5. Schnitt SJ, Moran MS, Giuliano AR. Lumpectomy Margins for Invasive Breast Cancer and Ductal Carcinoma in Situ: Current Guideline Recommendations, Their Implications, and Impact. J Clin Oncol. 2020; 38(20):2240-2245. doi: 10.1200/JCO.19.03213.

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.
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. doi: 10.1245/s10434-016-5446-2.

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
2. Fisher S, Yasui Y, Dabbs K, et al. (2018) Re-excision and survival following breast conserving surgery in early stage breast cancer patients: a population-based study. BMC Health Serv Res 18:94. 10.1186/s12913-018-2882-7
3. Kitchen PR, Cawson JN, Moore SE: Margins and outcome of screen-detected breast cancer with extensive in situ component. ANZ J Surg. 2006 Jul;76(7):591-5

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
5. McIntosh A, Freedman G, Eisenberg D: Recurrence rates and analysis of close or positive margins in patients treated without re-excision before radiation for breast cancer. Am J Clin Oncol. 2007 Apr;30(2):146-51.
6. Kurniawan ED, Wong MH, Windle I: Predictors of surgical margin status in breast-conserving surgery within a breast screening program. Ann Surg Oncol. 2008 Sep;15(9):2542-9.
7. Tamburelli F, Maggiorotto F, Marchio C, et al. (2020) Reoperation rate after breast conserving surgery as quality indicator in breast cancer treatment: A reappraisal. Breast 53:181-188. 10.1016/j.breast.2020.07.008

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)
3. Ha SM, Cha JH, Shin HJ et al. Mammography, US, and MRI to Assess Outcomes of Invasive Breast Cancer with Extensive Intraductal Component: A Matched Cohort Study. Radiology. 2019 Aug;292(2):299-308. doi: 10.1148/radiol.2019182762.



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Breast-Conserving Surgery (BCS): Surgical and Technical Aspects

	Oxford		
	LoE	GR	AGO
▪ Therapeutic stereotactic excision alone	4	D	--
▪ Intraoperative ultrasound to increase negative margin rates in non-palpable lesions	1a	A	+
▪ Intraoperative ultrasound to increase negative margins rates in palpable lesions (with smaller resection volumes)	1b	B	+
▪ Intraoperative margin evaluation (with Margin Probe®)	1b	A	+/-
▪ Specimen radiography and / or -sonography in non-palpable lesions and / or tumor-associated microcalcifications*	2b	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
2. Jacobs TW, Connolly JL, Schnitt SJ: Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? Am J Surg Pathol. 2002 Sep;26(9):1095-110
3. Plantade R, Hammou JC, Fighiera M: Underestimation of breast carcinoma with 11-gauge stereotactically guided directional vacuum-assisted biopsy. J Radiol. 2004 Apr;85(4 Pt 1):391-401
4. Jeevan R, Cromwell DA, Trivella M, et al. Reoperation rates after breast conserving surgery for breast cancer among women in England: retrospective study of hospital episode statistics. BMJ. 2012 Jul 12;345:e4505. doi: 10.1136/bmj.e4505.

Intraoperative ultrasound: Meta-analyses:

1. Athanasiou 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.

2. Ahmed M; Douek, M. Intra-operative ultrasound versus wire-guided localization in the surgical management of non-palpable breast cancers: systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013 Aug;140(3):435-46.
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
4. Banys-Paluchowski M, Rubio IT, Karadeniz Cakmak G et al. Intraoperative ultrasound-guided excision of non-palpable and palpable breast cancer: systematic review and meta-analysis. in press 2022

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.
3. Rahusen FD, Bremers AJ, Fabry HF, et al. (2002) Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. *Ann Surg Oncol* 9:994-998. 10.1007/BF02574518

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, Saria 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.

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.
3. Allweis TM, Kaufman Z, Lelcuk S et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. Am J Surg. 2008 Oct;196(4):483-9. doi: 10.1016/j.amjsurg.2008.06.024.

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.
5. Singletary: Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. Am J Surg. 2002 Nov;184(5):383-93.
6. Funk A, Heil J, Harcos A et al. Efficacy of intraoperative specimen radiography as margin assessment tool in breast conserving surgery. Breast Cancer Res Treat. 2020 Jan;179(2):425-433. doi: 10.1007/s10549-019-05476-6.



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Breast-Conserving Surgery (BCS) without Neoadjuvant Therapy

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

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

**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.

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*. 2014 Oct 16. pii: S1040-8428(14)00154-1. doi: 10.1016/j.critrevonc.2014.09.003. [Epub ahead of print]
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, Bournoux 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.

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

* Study participation recommended

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
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cN0 pN0(sn)(i+)LoE 1b A AGO –

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

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

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

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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	++
cN+**	pN+ _{oxa}	ycN0	ALND	+	ypN0 / ypN+	none	2b	B	++
			TAD	+	ypN0	none	2b	B	+
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
			SLNE	+/-	ypN0	none	2b	B	+/-
					ypN0 (i+)	ALND	2b	B	+/-
					ypN+ incl. ypN1mi	ALND	2b	B	+
		ycN+	ALND	++	ypN0 / ypN+	none	2b	B	++

* Study participation in EUBREAST-01 recommended; ** Study participation in AXSANA recommended



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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>In collaboration with:</p>  <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>				<h2 style="text-align: center;">Targeted Axillary Dissection (TAD)</h2> <h3 style="text-align: center;">= TLNE + SLNE</h3>		
				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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Factors Predicting Conversion from cN+ (before NACT) to ypN0

- **Young age**
- **Intrinsic subtype (TNBC, HER2 pos)**
- **Grade 3**
- **Ductal histology**
- **cN1 (vs. cN2)**
- **pCR (breast)**

Kantor et al. Ann Surg Oncol 2018

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Sentinel Lymph Node Excision (SLNE) Indications I			
	Oxford		
	LoE	GR	AGO
▪ Clinically / sonographically negative axilla (cN0)	1b	A	++
▪ cT 1–2	2b	A	++
▪ cT 3–4c	3b	B	+
▪ Multifocal / multicentric breast cancer	2b	B	+
▪ DCIS			
▪ Mastectomy	3b	B	+
▪ BCT	3b	B	-
▪ DCIS in male	5	D	+/-
▪ Male breast cancer	2b	B	+
▪ Omission of axillary intervention in elderly patients (≥ 70 yrs., co-morbidities, pT1, HR+)	3b	B	+/-

Statement: SLNE

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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, Shamlivan 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. Boughey 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.
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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.

Sentinel Lymph Node Excision (SLNE) Indications II			
	Oxford		
	LoE	GR	AGO
■ During pregnancy and / or breast feeding (only ^{99m} Tc-colloid, no blue dye)	3	C	++
■ After prior tumor excision	2b	B	+
■ After prior major breast surgery (e.g. reduction mammoplasty)	3b	C	+/-
■ Ipsilateral breast recurrence after prior BCS and prior SLNE	4	D	-
■ SLNE in the mammary internal chain	2b	B	-
■ After axillary surgery	3b	B	+/-
■ Prophylactic bilateral / contralateral mastectomy	3b	B	--
■ Inflammatory breast cancer	3b	C	-

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
2. Bergkvist L. Resolving the controversies surrounding lymphatic mapping in breast cancer. Future Oncol. 2008 Oct;4(5):681-8.
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Statement: internal mammarian

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2. Chen RC, Lin NU, Golshn M: Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review. J Clin Oncol. 2008 Oct 20;26(30):4981-9.
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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
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4. Ruano R, Ramos M, Garcia-Talavera JR: Staging the axilla with selective sentinel node biopsy in patients with previous excision of non-palpable and palpable breast cancer. Eur J Nucl Med Mol Imaging. 2008 Jul;35(7):1299-304.

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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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 patients [published online ahead of print, 2020 Jan 20]. *Breast Cancer Res Treat*. 2020;10.1007/s10549-020-05529-1.
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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
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Sentinel Lymph Node Excision (SLNE) Marking

Oxford		
LoE	GR	AGO
1a	A	++
1b	A	+
1a	A	+/-
2a	B	+/-
2a	B	+/-
4	D	-

- **^{99m}Tc Kolloid**
- **Preoperative lymphoscintigraphy (added information limited, but mandatory by legal regulations)***
- **Patent blue dye**
- **Indocyanin green (ICG)**
- **SPIO[#]**
- **Methylene blue**

* In Germany required for quality assurance of nuclear medicine

SPIO: Superparamagnetic Iron Oxide (Caveat: impaired MRI-sensitivity during follow-up)

Statement radiotracer/blue dye:

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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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-
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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
2. Thompson W, Argáez C. Ottawa (ON): Magnetic Localization System for Sentinel Lymph Node Biopsy: A Review of the Diagnostic Accuracy, Cost-Effectiveness, and Guidelines. Canadian Agency for Drugs and Technologies in Health; 2020

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.
2. Soni M, Saha S, Korant A, et al. A prospective trial comparing 1% lymphazurin vs 1% methylene blue in sentinel lymph node mapping

of gastrointestinal tumors. *Ann Surg Oncol*. 2009 Aug;16(8):2224-30.

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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.
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Statement: SPIO

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2. Rubio IT, Diaz-Botero S, Esgueva A, et al. The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer. *Eur J Surg Oncol*. 2015 Jan;41(1):46-51
3. Thill M, Kurylcio A, Welter R, et al. The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. Radioisotope. *Breast*. 2014 Apr;23(2):175-9.
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5. Thompson W, Argáez C. Magnetic Localization System for Sentinel Lymph Node Biopsy: A Review of the Diagnostic Accuracy, Cost-


Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Feb 26.

Statement: General

1. Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. *Lancet Oncol*. 2014 Jul;15(8):e351-62.

Statement: Comparisons


1. Jung SY, Kim SK, Kim SW, et al. Comparison of sentinel lymph node biopsy guided by the multimodal method of indocyanine green fluorescence, radioisotope, and blue dye versus the radioisotope method in breast cancer: a randomized controlled trial. *Ann Surg Oncol*. 2014 Apr;21(4):1254-9.
2. Sugie T, Sawada T, Tagaya N, et al. Comparison of the indocyanine green fluorescence and blue dye methods in detection of sentinel lymph nodes in early-stage breast cancer. *Ann Surg Oncol*. 2013 Jul;20(7):2213-8. doi: 10.1245/s10434-013-2890-0. Epub 2013 Feb 21.



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Surgical Approach in the Neoadjuvant Setting

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

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

Statement: clip marking

1. Kuerer HM, Singletary SE, Buzdar AU, et al. Surgical conservation planning after neoadjuvant chemotherapy for stage II and operable stage III breast carcinoma. Am J Surg. 2001 Dec;182(6):601-8.
2. Thomassin-Naggara I, Lalonde L, David J, et al. A plea for the biopsy marker: how, why and why not clipping after breast biopsy? Breast Cancer Res Treat. 2012 Apr;132(3):881-93.

Statement: operation and : tumor resection in new margins

1. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst. 2005 Feb 2;97(3):188-94.
2. Berruti A, Generali D, Kaufmann M, et al. International expert consensus on primary systemic therapy in the management of early breast cancer: highlights of the Fourth Symposium on Primary Systemic Therapy in the Management of Operable Breast Cancer, Cremona, Italy (2010). J Natl Cancer Inst Monogr. 2011;2011(43):147-51.
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5. Early Breast Cancer Trialists Collaborative Group. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: a metaanalysis of individual patient data from ten randomised trials. *Lancet Oncol* 2018;19(1):27-39

Statement: tumor free margins ...

1. Cendán JC et al., Accuracy of Intraoperative Frozen-Section Analysis of Breast Cancer Lumpectomy-Bed Margins. *J Am Coll Surg* 2005;201:194–198.
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3. Ciccarelli G, Di Virgilio MR, Menna S. Radiography of the surgical specimen in early stage breast lesions: diagnostic reliability in the analysis of the resection margins. *Radiol Med (Torino)*. 2007 Apr;112(3):366-76.
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7. Buchholz TA, Somerfield MR, Griggs JJ et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. *J Clin Oncol*. 2014 May 10;32(14):1502-6.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from randomised trials. (published online Dec 11.) *Lancet Oncol*. 2017; [http://dx.doi.org/10.1016/S1470-2045\(17\)30777-5](http://dx.doi.org/10.1016/S1470-2045(17)30777-5)

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

Statement: Timing of radiation and chemotherapy

1. Piroth MD, Pinkawa M, Gagel B et al. Sequencing chemotherapy and radiotherapy in locoregional advanced breast cancer patients after mastectomy - a retrospective analysis. BMC Cancer. 2008 Apr 23;8:114.
2. Tsoutsou PG, Koukourakis MI, Azria D, Belkacémi Y. et al. Optimal timing for adjuvant radiation therapy in breast cancer: a comprehensive review and perspectives. Crit Rev Oncol Hematol. 2009;71(2):102-16.
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4. Karlsson P, Cole BF, Colleoni M, et al; International Breast Cancer Study Group; Timing of radiotherapy and outcome in patients receiving adjuvant endocrine therapy. Int J Radiat Oncol Biol Phys. 2011;80(2):398-402.

Statement: Tamoxifen concurrent with chemotherapy

1. Adamowicz K, Marczevska M, Jassem J. Combining systemic therapies with radiation in breast cancer. Cancer Treat Rev. 2009 Aug;35(5):409-16
2. Harris EE, Christensen VJ, Hwang WT, et al. Impact of concurrent versus sequential tamoxifen with radiation therapy in early-stage breast cancer patients undergoing breast conservation treatment. J Clin Oncol. 2005 Jan 1;23(1):11-6.
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cancer. J Clin Oncol. 2005 Jan 1;23(1):24-9.

Statement A1 concurrent with radiotherapy

1. Azria D, Belkacemi Y, Romieu G, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for early-stage breast cancer (CO-HO-RT): a phase 2 randomised trial. Lancet Oncol 2010;11(3):258-65
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3. Ishitobi M, Shiba M, Nakayama T, et al. Treatment sequence of aromatase inhibitors and radiotherapy and long-term outcomes of breast cancer patients. Anticancer Res. 2014;34(8):4311-4.