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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Pathology



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■

Versions 2004–2021:

**Blohmer / Costa / Fehm / Friedrichs / Harbeck / Huober /
Kreipe / Lück / Maass / Schmidt / Schneeweiss/ Sinn / Thomssen**

■

Version 2022:

Sinn / Huober / Kreipe

Screened data bases: PubMed 2021

Search Query:

(Breast Diseases/PA[mh] AND ("2011/01/01"[dp] : "2021/12/31"[dp])) AND ("english"[la] OR "german"[la])

Guidelines screened

1. WHO, Classification of Tumours Editorial Board. Breast Tumours: WHO Classification of Tumours Lyon (France): International Agency for Research on Cancer; 2019. DOI: 10.1111/his.14091
2. National Comprehensive Cancer Network (NCCN). Breast Cancer (Version 2.2022). http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed Jan 01, 2022
3. Burstein, H. J. *et al.* Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol* 32, 1216–1235 (2021).
4. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. (2021). https://www.awmf.org/uploads/tx_szleitlinien/032-045OLI_S3_Mammakarzinom_2021-07.pdf Accessed Jan 01, 2022
5. Wells CA. Pathology_Update_Breast_Screening. 2014:1-48. <http://www.euref.org/downloads?download=24:european->

guidelines-for-quality-assurance-in-breast-cancer-screening-and-diagnosis-pdf

6. The Royal College of Pathologists. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. June 2016:1-160. <https://www.rcpath.org/resourceLibrary/g148-breastdataset-hires-jun16-pdf.html>
7. Schweizerische Gesellschaft für Pathologie (2017). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. https://sgpath.ch/docs/QRL/QRL_SGPath_Mamma_2017.pdf

Preanalytics: Fixation			
	Oxford		
	LoE	GR	AGO
▪ Minimize time to fixation (cold ischemia time)	5	D	++
▪ Minimal fixation time of 6 hours for optimal antigen preservation	5	D	++
▪ Optimal fixation time 6 - 72 h for core biopsies	5	D	++
▪ Optimal fixation time for resection specimens: 12 - 72 h	5	D	++
▪ Use of neutral buffered formalin	5	D	++


Antigen preservation

1. Apple, S., Pucci, R., Lowe, A. C., et al. (2011). The effect of delay in fixation, different fixatives, and duration of fixation in estrogen and progesterone receptor results in breast carcinoma. *American Journal of Clinical Pathology*, 135(4), 592–598.
2. De Cecco, L., Musella, V., Veneroni, S., et al. (2009). Impact of biospecimens handling on biomarker research in breast cancer. *BMC Cancer*, 9, 409. <http://doi.org/10.1186/1471-2407-9-409>
3. Kalkman, S., Barentsz, M. W., & van Diest, P. J. (2014). The Effects of Under 6 Hours of Formalin Fixation on Hormone Receptor and HER2 Expression in Invasive Breast Cancer: A Systematic Review. *American Journal of Clinical Pathology*, 142(1), 16–22.
4. Lee, A. H. S., Key, H. P., et al. (2014). The effect of delay in fixation on HER2 expression in invasive carcinoma of the breast assessed with immunohistochemistry and in situ hybridisation. *Journal of Clinical Pathology*, 67(7), 573–575
5. Nagahashi, M., Shimada, Y., Ichikawa, H. et al. (2017). Formalin-fixed paraffin-embedded sample conditions for deep next generation sequencing. *The Journal of Surgical Research*, 220, 125–132. <http://doi.org/10.1016/j.jss.2017.06.077>
6. Portier, B. P., Wang, Z., Downs-Kelly, E., et al. (2013). Delay to formalin fixation “cold ischemia time”: effect on ERBB2 detection by in-situ hybridization and immunohistochemistry. *Modern Pathology*, 26(1), 1–9. doi:10.1038/modpathol.2012.123
7. Wolff, A. C., Hammond, M. E. H., Allison, K. H. et al. (2018). Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Archives of Pathology & Laboratory Medicine*, arpa.2018–0902–SA. <http://doi.org/10.5858/arpa.2018-0902-SA>

8. Yildiz-Aktas, I. Z., Dabbs, D. J., & Bhargava, R. (2012). The effect of cold ischemic time on the immunohistochemical evaluation of estrogen receptor, progesterone receptor, and HER2 expression in invasive breast carcinoma. *Modern Pathology*, 25(8), 1098–1105. <http://doi.org/10.1038/modpathol.2012.59>

Retraction artifacts

1. Ragage, F., Debled, M., MacGrogan, G., et al. (2010). Is it useful to detect lymphovascular invasion in lymph node-positive patients with primary operable breast cancer? *Cancer*, 116(13), 3093–3101.
2. Lester, S. C., Bose, S., Chen, Y.-Y., et al. (2009). Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*, 133(10), 1515–1538.



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Use of Breast Cytology*


Oxford		
LoE	GR	AGO
5	D	+
5	D	-
5	D	+/-
5	D	+/-

- Nipple secretion
- Tumor*
- Cyst
- Lymph node

* Ultrasound-guided core biopsy recommended

1. Day, C, N Moatamed, AM Fimbres, et al: A Retrospective Study of the Diagnostic Accuracy of Fine-Needle Aspiration for Breast Lesions and Implications for Future Use. *Diagnostic Cytopathology* 36, no. 12 (November 30, 2008): 855–60.
2. Pinder, S E, and J S Reis-Filho. Non-Operative Breast Pathology. *Journal of Clinical Pathology* 60, no. 12 (December 20, 2006): 1297–99. doi:10.1136/jcp.2006.040519.
3. Tse, G M K, T K F Ma, P C W Lui, et al. Fine Needle Aspiration Cytology of Papillary Lesions of the Breast: How Accurate Is the Diagnosis?. *Journal of Clinical Pathology* 61, no. 8 (August 2008): 945–49. doi:10.1136/jcp.2008.057489.
4. Ibrahim AE, Bateman AC, Theaker JM, et al. The role and histological classification of needle core biopsy in comparison with fine needle aspiration cytology in the preoperative assessment of impalpable breast lesions. *J Clin Pathol* 2001;54:121–5.
5. He, X., Wang, Y., Nam, G., et al. (2018). A 10 year retrospective review of fine needle aspiration cytology of cystic lesions of the breast with emphasis on papillary cystic lesions. *Diagnostic Cytopathology*. <http://doi.org/10.1002/dc.24123>
6. Bruzzzone, M., Saro, F., Bruno, S. et al. (2018). Synergy of cytological methods in the pathological staging of breast cancer: Axillary fine-needle aspiration and intraoperative scrape cytology of the sentinel lymph node. *Diagnostic Cytopathology*, 46(11), 919–926. <http://doi.org/10.1002/dc.23995>
7. Tiwari, P., Ghosh, S., & Agrawal, V. K. (2018). Evaluation of breast lesions by digital mammography and ultrasound along with fine-needle aspiration cytology correlation. *Journal of Cancer Research and Therapeutics*, 14(5), 1071–1074.

<http://doi.org/10.4103/0973-1482.191053>

Workup: Core Needle Biopsies (US-Guided or Stereotactic)			
	Oxford		
	LoE	GR	AGO
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▪ Routine workup in step sections (14G: 1–3 step sections / 11G, 8G: 6–8 step sections)	5	D	++
▪ Correlation with imaging (density, calcifications), use of B-classification	1b	B	++
▪ Frozen section diagnosis on core biopsies	5	D	--
▪ Routine evaluation of ER / PR and HER2 status	3b	C	++
▪ Turn-around time < 24 h (histology)	5	D	+

Statement: Routine workup in step sections

1. Hahn, M., Krainick-Strobel, U., Toellner, T. et al. (2012). Interdisciplinary consensus recommendations for the use of vacuum-assisted breast biopsy under sonographic guidance: first update 2012. *Ultraschall Med*, 33(4), 366–371. <http://doi.org/10.1055/s-0032-1312831>
2. Sinn, Gerber, Brucker et al. (2017): DCIS und Risikoläsionen. In: AWMF: S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, S. 79 - 89.

Statement: Correlation with imaging

1. Heywang-Köbrunner SH, Sinnatamby R, Lebeau A, et al; Consensus Group. Interdisciplinary consensus on the uses and technique of MR-guided vacuum-assisted breast biopsy (VAB): results of a European consensus meeting. *Eur J Radiol*. 2009 Nov;72(2):289-94
2. Sinn, Gerber, Brucker et al. (2017): DCIS und Risikoläsionen. In: AWMF: S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, S. 79 - 89.

Statement: Frozen section diagnosis on core biopsies

1. Lebeau, Gerber, Brucker et al. (2017): Pathomorphologische Untersuchung. In: AWMF: S3-Leitlinie Früherkennung, Diagnostik,

Therapie und Nachsorge des Mammakarzinoms, S. 100 - 139.

2. Dämmrich, M., Thomssen, C., Hillemanns, P. et al. (2012). Intraoperative pathologische Sofortuntersuchung in der Mammachirurgie. *Der Pathologe*, 33(5), 424–429. <http://doi.org/10.1007/s00292-012-1596-6>

Statement: Routine evaluation of ER/PgR and HER-2 status

1. Dekker, T. J. A., Smit, V. T. H. B. M., Hooijer, G. K. J. et al. (2013). Reliability of core needle biopsy for determining ER and HER2 status in breast cancer. *Annals of Oncology*, 24(4), 931–937. <http://doi.org/10.1093/annonc/mds599>
2. Meattini, I., Bicchierai, G., Saieva, C. et al. (2017). Impact of molecular subtypes classification concordance between preoperative core needle biopsy and surgical specimen on early breast cancer management: Single-institution experience and review of published literature. *European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, 43(4), 642–648. <http://doi.org/10.1016/j.ejso.2016.10.025>

Statement: Turn-around time < 24h

1. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (eds) European guidelines for quality assurance in breast cancer

Workup: Breast-Conserving Specimens			
	Oxford		
	LoE	GR	AGO
▪ Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)	5	D	++
▪ Systematic sampling, at least 1 tissue block every 1 cm	5	D	++
▪ Inking of resection margins. Sampling of resection margins	5	D	++
▪ Documentation after slicing using specimen radiography, photo documentation or diagram	5	D	+


Guidelines

1. The Royal College of Pathologists. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. June 2016:1-160. <https://www.rcpath.org/profession/publications/cancer-datasets.html>.
2. Schnitt SJ, Moran MS, Houssami N, Morrow M. The 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: Perspectives for Pathologists. *Arch Pathol Lab Med*. August 2014. doi:10.5858/arpa.2014-0384-ED.
3. Schweizerische Gesellschaft für Pathologie (2002). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. https://sgpath.ch/docs/QRL/QRL_SGPath_Mamma_2017.pdf
4. Lester SC, Bose S, Chen Y-Y, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*. 2009;133(10):1515-1538. doi:10.1043/1543-2165-133.10.1515.
5. Lester SC, Bose S, Chen Y-Y, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. *Arch Pathol Lab Med*. 2009;133(1):15-25. doi:10.1043/1543-2165-133.1.15.
6. Fitzgibbons P, Connolly J, Page D. Updated protocol for the examination of specimens from patients with carcinomas of the

breast. Cancer Committee. *Arch Pathol Lab Med*. 2000;124(7):1026-1033.

Systematic Sampling

1. Ang SC, Tapia G, Davidson EJ, et al. Positive anterior margins in breast conserving surgery: Does it matter? A systematic review of the literature. *Breast*. 2016;27:105-108. doi:10.1016/j.breast.2015.12.013.
2. Molina MA, Snell S, Franceschi D, et al. Breast specimen orientation. *Ann Surg Oncol*. 2009;16(2):285-288. doi:10.1245/s10434-008-0245-z.
3. Sinn HP, Anton HW, Magener A, Fournier von D, Bastert G, Otto HF. Extensive and predominant in situ component in breast carcinoma: their influence on treatment results after breast-conserving therapy. *Eur J Cancer*. 1998;34(5):646-653. doi:10.1016/s0959-8049(97)10106-x.
4. Decker T, Ruhnke M, Schneider W. Standardisierte pathologische Untersuchung von Mamma-Exzisionspräparaten. Relevanz innerhalb eines interdisziplinären Praxisprotokolls für das Qualitätsmanagement der brusterhaltenden Therapie. *Der Pathologe*. 1997;18(1):53-59. doi:10.1007/s002920050196.



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Workup: Mastectomy Specimens

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Margins always to be sampled <ul style="list-style-type: none"> ▪ Skin close to tumor ▪ Deep margin ▪ Other margins, if close (< 1 cm) 	5	D	++
▪ Attention to soft tissue margins in skin sparing mastectomy	5	D	++
▪ Routine sampling of uninvolved quadrants, skin above tumor and retroareolar region	5	D	++
▪ Systematic sampling in prophylactic mastectomies (patients with BRCA-1/2 mutation)	5	D	++

Guidelines

1. The Royal College of Pathologists. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. June 2016:1-160. <https://www.rcpath.org/profession/publications/cancer-datasets.html>.
2. Schnitt SJ, Moran MS, Houssami N, Morrow M. The 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: Perspectives for Pathologists. *Arch Pathol Lab Med*. August 2014. doi:10.5858/arpa.2014-0384-ED.
3. Schweizerische Gesellschaft für Pathologie (2002). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. https://sgpath.ch/docs/QRL/QRL_SGPath_Mamma_2017.pdf
4. Lester SC, Bose S, Chen Y-Y, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*. 2009;133(10):1515-1538. doi:10.1043/1543-2165-133.10.1515.
5. Lester SC, Bose S, Chen Y-Y, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. *Arch Pathol Lab Med*. 2009;133(1):15-25. doi:10.1043/1543-2165-133.1.15.
6. Fitzgibbons P, Connolly J, Page D. Updated protocol for the examination of specimens from patients with carcinomas of the

breast. Cancer Committee. *Arch Pathol Lab Med*. 2000;124(7):1026-1033.

Skin sparing and nipple sparing mastectomy

1. Papassotiropoulos B, Güth U, Chiesa F, et al. Prospective Evaluation of Residual Breast Tissue After Skin- or Nipple-Sparing Mastectomy: Results of the SKINI-Trial. *Ann Surg Oncol*. 2019;26(5):1254-1262. doi:10.1245/s10434-019-07259-1.
2. Mota BS, Riera R, Ricci MD, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. *Cochrane Database Syst Rev*. 2016;11:CD008932. doi:10.1002/14651858.CD008932.pub3.
3. Zhang H, Li Y, Moran MS, Haffty BG, Yang Q. Predictive factors of nipple involvement in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2015;151(2):239-249. doi:10.1007/s10549-015-3385-4.
4. Wang J, Xiao X, Wang J, et al. Predictors of nipple-areolar complex involvement by breast carcinoma: histopathologic analysis of 787 consecutive therapeutic mastectomy specimens. *Ann Surg Oncol*. 2012;19(4):1174-1180. doi:10.1245/s10434-011-2107-3.
5. Petit JY, Veronesi U, Orecchia R, et al. Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. *Ann Oncol*. January 2012. doi:10.1093/annonc/mdr566.
6. Weidong Li, Shuling Wang, Xiaojing Guo, et al. Nipple involvement in breast cancer: retrospective analysis of 2323 consecutive mastectomy specimens. *International Journal of Surgical Pathology*. 2011;19(3):328-334. doi:10.1177/1066896911399279.
7. Brachtel EF, Rusby JE, Michaelson JS, et al. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009;27(30):4948-4954. doi:10.1200/JCO.2008.20.8785.
8. Güth U, Wight E, Schötzau A, et al. Correlation and significance of histopathological and clinical features in breast cancer with skin involvement (T4b). *Hum Pathol*. 2006;37(3):264-271.
9. Torresan RZ, Santos dos CC, Okamura H, Alvarenga M. Evaluation of residual glandular tissue after skin-sparing mastectomies. *Ann Surg Oncol*. 2005;12(12):1037-1044. doi:10.1245/ASO.2005.11.027.
10. Torresan RZ, Cabello dos Santos C, Brenelli H, Okamura H, Alvarenga M. Residual glandular tissue after skin-sparing mastectomies. *Breast J*. 2005;11(5):374-375. doi:10.1111/j.1075-122X.2005.00029.x.
11. Sikand K, Lee AHS, Pinder SE, Elston CW, Ellis IO. Sections of the nipple and quadrants in mastectomy specimens for carcinoma are of limited value. *SciMed Central*. 2005;58(5):543-545. doi:10.1136/jcp.2004.022665.

12. Love SM, Barsky SH. Anatomy of the nipple and breast ducts revisited. *Cancer*. 2004;101(9):1947-1957. doi:10.1002/cncr.20559.
13. Ho CM, Mak CKL, Lau Y, Cheung WY, Chan MCM, Hung WK. Skin involvement in invasive breast carcinoma: safety of skin-sparing mastectomy. *Ann Surg Oncol*. 2003;10(2):102-107. doi:10.1245/aso.2003.05.001.
14. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Ann Surg Oncol*. 2002;9(2):165-168.
15. Santini D, Taffurelli M, Gelli MC, et al. Neoplastic involvement of nipple-areolar complex in invasive breast cancer. *Am J Surg*. 1989;158(5):399-403.
16. Lüttges J, Kalbfleisch H, Prinz P. Nipple involvement and multicentricity in breast cancer. A study on whole organ sections. *J Cancer Res Clin Oncol*. 1987;113(5):481-487.
17. Morimoto T, Komaki K, Inui K, et al. Involvement of nipple and areola in early breast cancer. *Cancer*. 1985;55(10):2459-2463.

Workup: Sentinel Node Biopsy			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Full workup using step sections of $\leq 500 \mu\text{m}$ on paraffin embedded tissue 	5	D	++
<ul style="list-style-type: none"> Cytokeratin immunohistochemistry <ul style="list-style-type: none"> If suspicious, to detect micrometastases 	2b	B	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> For micrometastasis detection after NACT 	2b	B	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> As a routine procedure 	5	D	+/-
<ul style="list-style-type: none"> Frozen section (compromises paraffin histomorphology) <ul style="list-style-type: none"> If clinical consequences 	5	D	+
<ul style="list-style-type: none"> <ul style="list-style-type: none"> If no clinical consequences from frozen section (e.g. cT1 or cT2 and cN0 and BCT) 	5	D	-
<ul style="list-style-type: none"> Imprint cytology instead of, or in addition to frozen section 	3b	C	+/-
<ul style="list-style-type: none"> RT-PCR for epithelial genes <ul style="list-style-type: none"> OSNA 	4	D	-
	3b	B	-

Statement: Evaluation of sentinel node biopsy

- Maguire, A., & Brogi, E. (2016). Sentinel lymph nodes for breast carcinoma: an update on current practice. *Histopathology*, 68(1), 152–167. <http://doi.org/10.1111/his.12853>
- Liu L-C, Lang JE, Lu Y, et al. Intraoperative frozen section analysis of sentinel lymph nodes in breast cancer patients: a meta-analysis and single-institution experience. *Cancer*. 2011;117(2):250-258. doi:10.1002/cncr.25606.

Statement: Full workup using step sections of $\geq 500 \mu\text{m}$ on paraffin embedded tissue

- Maguire, A., & Brogi, E. (2016). Sentinel lymph nodes for breast carcinoma: an update on current practice. *Histopathology*, 68(1), 152–167. <http://doi.org/10.1111/his.12853>

Statement: Frozen section

- Langer, I., Guller, U., Berclaz, G. et al. (2009). Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study. *Breast Cancer Research and Treatment*, 113(1), 129–136. <http://doi.org/10.1007/s10549-008-9911-x>

Statement: Imprint cytology instead or in addition of frozen section

1. Layfield et al. Intraoperative assessment of sentinel lymph nodes in breast cancer. *The British journal of surgery* (2011) vol. 98 (1) pp. 4-17
2. Upender, S., Mohan, H., Handa, U. et al. (2009). Intraoperative evaluation of sentinel lymph nodes in breast carcinoma by imprint cytology, frozen section and rapid immunohistochemistry. *Diagnostic Cytopathology*, 37(12), 871–875. <http://doi.org/10.1002/dc.21120>

Statement: RT-PCR for epithelial genes

1. Layfield, D. M., Agrawal, A., Roche, H. et al. (2011). Intraoperative assessment of sentinel lymph nodes in breast cancer. *The British Journal of Surgery*, 98(1), 4–17. <http://doi.org/10.1002/bjs.7229>
2. Visser, M., Jiwa, M., Horstman, A. et al. (2008). Intra-operative rapid diagnostic method based on CK19 mRNA expression for the detection of lymph node metastases in breast cancer. *International Journal of Cancer Journal International Du Cancer*, 122(11), 2562–2567. <http://doi.org/10.1002/ijc.23451>

Workup: Intraoperative Pathological Evaluation and Frozen Sections			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Sentinel node biopsy for invasive cancer (compromises final paraffin histomorphology) <ul style="list-style-type: none"> ■ If clinical consequences ■ No clinical consequences ■ Closest margin of resection <ul style="list-style-type: none"> ■ If macroscopically < 1 cm ■ If macroscopically > 1 cm ■ Lesions ≥ 1 cm, without core biopsy ■ Non-palpable lesions or lesions < 1 cm ■ Conservation of fresh tissue (tumor banking) 	5	D	+
	5	D	-
	5	D	+
	5	D	-
	5	D	+
	5	D	-
	5	D	+

Statement: Sentinel node biopsy for invasive cancer

1. Kühn T, Bembenek A, Decker T et al. A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer 2005; 103: 451-461.
2. Grabau D, Rank F, Friis E. Intraoperative frozen section examination of axillary sentinel lymph nodes in breast cancer. APMIS 2005; 113: 7-12.
3. Van Diest PJ, Torrença H, Borgstein PJ et al. Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. Histopathology 1999; 35: 14-18.

Statement: Closest margin of resection

1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthal R, Helfer L, Hrsg.). <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>
2. Kraus-Tiefenbacher U, Scheda A, Steil V, et al. Intraoperative radiotherapy (IORT) for breast cancer using the Intrabeam system. Tumori. 2005;91:339-45

Statement: Lesions ≥ 1 cm, without core biopsy


1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthal R, Helfer L, Hrsg.). <http://www.ago->

manual.at/inhalt/i-mammakarzinom/15-pathologie/

2. Fitzgibbons PL, Connolly JL, Page DL. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Arch Pathol Lab Med 2000; 124:1026- 1033. (ACR)
3. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, et al (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006, pp 256-311

Statement: Non-palpable lesions or lesions < 1 cm

1. Morrow M, Strom E, Bassett L et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). CA Cancer J Clin 2002; 52: 256-276.



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Reporting: Histologic Tumor Type

- **Histologic tumor typing according to WHO-Classification, (5th ed., 2019)**
 - **Partial special differentiation:**
> 50 % NST component
and < 50 % special tumor type (minor component)
 - **Mixed differentiation:**
> 50 % special tumor type
and < 50 % NST component
Example: mucinous breast cancer, mixed type
 - **Pure types:**
> 90 % special tumor type
Examples: tubular or cribriform Ca.

Oxford		
LoE	GR	AGO
3b	C	++


WHO-Classification

1. Hoon TP, Ellis I, Allison K, et al. The 2019 WHO classification of tumours of the breast. *Histopathology*. February 2020. doi:10.1111/his.14091.
2. WHO. Breast Tumours: WHO Classification of Tumours. 5 ed. Lyon (France): International Agency for Research on Cancer; 2019.
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	Ductal TNBC: Comparable Survival Rates and Similar Response Rates to Chemotherapy for ER = 0 % Compared to ER 1 % - < 10 %		
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	<p>Villegas, S. L. <i>Eur J Cancer</i> 148, 159–170 (2021) DOI: 10.1016/j.eyjca.2021.02.020</p>	<p>Neoadjuvant clinical trial cohorts (n = 2765) comparing neg. ER/PR (< 1%) vs. ER/PR low pos. (ER and/or PR < 9%) vs. strong-pos. (ER or PR ≥ 10%) HR expression.</p>	<p>Low HR-positive, HER2-negative tumours had a similar clinical behavior compared to TNBC, showing high pCR rates and poor survival and also a basal-like gene expression signature. Patients with low HR-positive tumours should be regarded as candidates for therapy strategies targeting TNBC.</p>
	<p>Dieci, M. V. et al. <i>Npj Breast Cancer</i> 7, 101 (2021) DOI: 10.1038/s41523-021-00308-7</p>	<p>406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).</p>	<p>No difference was observed in overall survival (OS) according to ER expression levels (5-years OAS 82.3% vs. 76.7% for ER-negative and ER-low positive BC, respectively, p = 0.8). Our results suggest the use of a 10% cut-off, rather than <1%, to define triple-negative BC (TNBC).</p>
	<p>Reddy, S. M. et al. <i>British Journal of Cancer</i> 118, 17–23 (2018) DOI: 10.1038/bjc.2017.379</p>	<p>Stage I-III TNBC pat. (n = 873) who were disease free at 5 years from diagnosis. Recurrence-free interval (RFI), r.f. survival (RFS), and distant r.f. survival (DRFS) rates were calculated.</p>	<p>After a disease-free interval of 5 years, patients with low hormone receptor-pos. cancers had a higher risk of late events as measured by RFS, and similar risk by RFI or DRFS, compared to TNBC survivors.</p>

Chemotherapy response and survival in low-ER BC vs. TNBC

1. Villegas, S. L. *et al.* Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors – An analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer* **148**, 159–170 (2021).
2. Dieci, M. V. *et al.* Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. *Npj Breast Cancer* **7**, 101 (2021).
3. Reddy, S. M. *et al.* Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. *British Journal of Cancer* **118**, 17–23 (2018).



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Rare Histological TNBC Subtypes Show Divergent Tumor Differentiation Patterns and Clinical Behavior

Apocrine TNBC

- Luminal phenotype (no basal markers)
- High expression of the androgen receptor
- Low tumor proliferation
- Poor response to chemotherapy
- Better prognosis than ductal TNBC

Metaplastic TNBC



- See chapter 15 Special Situations

Rare and salivary-type TNBC

- Tumors with divergent clinical behavior and specific genetic alterations
- Mostly low tumor proliferation
- Poor response to conventional chemotherapy
- Experimental treatment according to the molecular pathology (e.g. NTREK for secretory ca.)


Rare histological TNBC subtypes

1. Cserni, G. *et al.* Triple-Negative Breast Cancer Histological Subtypes with a Favourable Prognosis. *Cancers* 13, 5694 (2021).
2. Cima, L. *et al.* Triple-negative breast carcinomas of low malignant potential: review on diagnostic criteria and differential diagnoses. *Virchows Arch* 1–18 (2021) doi:10.1007/s00428-021-03174-7.
3. Schnitt, S. J., Fend, F. & Decker, T. Breast carcinomas of low malignant potential. *Virchows Arch* 1–15 (2021) doi:10.1007/s00428-021-03163-w.
4. Mills, M. N. *et al.* Histologic heterogeneity of triple negative breast cancer: A National Cancer Centre Database analysis. *European journal of cancer (Oxford, England : 1990)* 98, 48–58 (2018).
5. Kandil, D. & Khan, A. Triple negative breast carcinoma: the good, the bad and the ugly. *Diagnostic Histopathology* 18, 210–216 (2012).
6. Montagna, E. *et al.* Heterogeneity of triple-negative breast cancer: histologic subtyping to inform the outcome. *Clinical breast cancer* 13, 31–39 (2013).

<div>  Apocrine TNBC: More Favorable Survival and Poor Response to Adjuvant Chemotherapy </div>			
<div>  </div>			
<p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	Reference	Patients	Results
	Saridakis, A. <i>et al.</i> <i>Ann Surg Oncol</i> 28 , 5610–5616 (2021). DOI: 10.1245/s10434-021-10518-9	Women with invasive apocrine cancer were retrospectively identified from the Surveillance, Epidemiology, and End Results (SEER) database. N = 533 triple-negative apocrine cancers were identified.	Half of apocrine tumors are triple negative, but these have more favorable features and much better survival than non-apocrine triple-negative cancers. Compared with non-apocrine triple-negative, apocrine triple-negative patients were much older, with smaller, lower-grade tumors and much better survival (86% vs. 74%).
	Montagna, E. <i>et al.</i> <i>Breast</i> 53 , 138–142 (2020). DOI: 10.1038/s41523-021-00308-7	406 patients with ER < 10% HER2-negative BC. Pat. Were categorized in ER-negative (ER < 1%; N = 364) and ER-low positive (1–9%, N = 42).	The outcome of selected apocrine triple negative breast cancer patients who did not received adjuvant chemotherapy is excellent and supports a treatment de-escalation.
	Mills, A. M., <i>et al.</i> <i>Am J Surg Pathol</i> 40 , 1109–1116 (2016). DOI: 10.1097/pas.0000000000000671	All pure apocrine carcinomas diagnosed during a 10-year period were reviewed, and clinicopathologic characteristics were compared with a control group of 26 non-apocrine TNBC cases. Twenty apocrine carcinomas were identified (~ 0.8% of all breast cancers).	Apocrine TNBC had a favorable clinical prognosis, with 80% of patients showing no evidence of disease-related morbidity or mortality (mean follow-up: 45.2 mo). Pure apocrine carcinomas represent a clinicopathologically distinct subgroup of triple-negative breast cancer characterized by AR positivity.

Apocrine TNBC

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2. Montagna, E. *et al.* Prognosis of selected triple negative apocrine breast cancer patients who did not receive adjuvant chemotherapy. *Breast Official J European Soc Mastology* **53**, 138–142 (2020).
3. Mills, A. M., Gottlieb, C. E., Wendroth, S. M., Brenin, C. M. & Atkins, K. A. Pure Apocrine Carcinomas Represent a Clinicopathologically Distinct Androgen Receptor-Positive Subset of Triple-Negative Breast Cancers. *The American journal of surgical pathology* **40**, 1109–1116 (2016).
4. Vranic, S. *et al.* Apocrine carcinoma of the breast: a comprehensive review. *Histology and histopathology* **28**, 1393–1409 (2013).


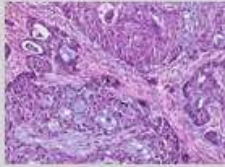
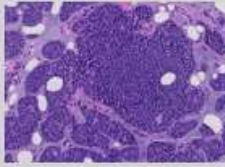
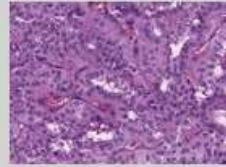


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Rare and Salivary-Type TNBC: Tumors with Divergent Clinical Behavior and Specific Genetic Alterations

Adenoid-cystic carcinoma	Secretory carcinoma	Polymorphous carcinoma	Tall cell carcinoma with reversed polarity
			
MYB-NFIB MYBL1 rearrangements MYB gene amplification	ETV6-NTRK3 gene fusions	PRKD1 E710D PRKD1 / PRKOZ / PRKD3 rearrangements	IDH2 hotspot mutations

Adenoid-cystic carcinoma

1. Kim, J. et al. MYBL1 rearrangements and MYB amplification in breast adenoid cystic carcinomas lacking the MYB-NFIB fusion gene. *The Journal of Pathology* 244, 143–150 (2018).
2. Fusco, N. et al. Genetic events in the progression of adenoid cystic carcinoma of the breast to high-grade triple-negative breast cancer. *Modern Pathology* 29, 1292–1305 (2016).
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5. Wetterskog, D. et al. Adenoid cystic carcinomas constitute a genomically distinct subgroup of triple-negative and basal-like breast cancers. *The Journal of Pathology* 226, 84–96 (2012).

Secretory carcinoma

1. Amott, D. H., Masters, R. & Moore, S. Secretory carcinoma of the breast. *The breast journal* 12, 183 (2006).
2. Laé, M. et al. Secretory breast carcinomas with ETV6-NTRK3 fusion gene belong to the basal-like carcinoma spectrum. *Modern Pathology* 22, 291–298 (2008).
3. Skálová, A. et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *The American journal of surgical pathology* 34, 599–608 (2010).

8. Castillo, M. D. *et al.* Secretory Breast Carcinoma: A Histopathologic and Genomic Spectrum Characterized by a Joint Specific ETV6-NTRK3 Gene Fusion. *The American journal of surgical pathology* 39, 1458–1467 (2015).
9. Soyer, T. *et al.* Secretory breast carcinoma in a 6-year-old girl: mastectomy with sentinel lymph node dissection. *Pediatric surgery international* 31, 677–681 (2015).

Polymorphous carcinoma

1. Skálová, A. *et al.* The Role of Molecular Testing in the Differential Diagnosis of Salivary Gland Carcinomas. *Am J Surg Pathology* 42, e11–e27 (2018).
2. Asioli, S. *et al.* Polymorphous adenocarcinoma of the breast. Report of three cases. *Virchows Arch* 448, 29–34 (2006).

Tall cell carcinoma with reversed polarity

1. Chiang, S. *et al.* IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity. *Cancer Research* 76, 7118–7129 (2016).
2. Tosi, A. L. *et al.* Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma: Report of 4 Cases With Evidence of Malignant Potential. *International Journal of Surgical Pathology* 15, 14–19 (2016).
3. Pitino, A., Squillaci, S., Spairani, C., Rassu, P. C. & Cosimi, M. F. Tall cell variant of papillary breast carcinoma: an additional case with review of the literature. *Pathologica* 109, 162–167 (2017).
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7. Lozada, J. R. *et al.* Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms (solid papillary carcinomas with reverse polarity) harbour recurrent mutations affecting IDH2 and PIK3CA: a validation cohort. *Histopathology* 73, 339–344 (2018).
8. hong, E. *et al.* Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma: Molecular Characterization by Next-

Generation Sequencing and Histopathological Comparison With Tall Cell Papillary Carcinoma of Thyroid. *International Journal of Surgical Pathology* 27, 1066896918800779–141 (2018).

9. Asioli, S. & Ambrosi, F. Tall Cell Variant of Papillary Breast Carcinoma. in vol. 14 371–374 (Springer International Publishing, 2019).
10. Zhong, E. *et al.* Breast Tumor Resembling the Tall Cell Variant of Papillary Thyroid Carcinoma: Molecular Characterization by Next-Generation Sequencing and Histopathological Comparison With Tall Cell Papillary Carcinoma of Thyroid. *International Journal of Surgical Pathology* 27, 1066896918800779–141 (2018).
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12. Osako, T., Takeuchi, K., Horii, R., Iwase, T. & Akiyama, F. Secretory carcinoma of the breast and its histopathological mimics: value of markers for differential diagnosis. *Histopathology* 63, 509–519 (2013).
13. Asioli, S. *et al.* Polymorphous adenocarcinoma of the breast. Report of three cases. *Virchows Arch* 448, 29–34 (2006).

Reporting: Grade of Malignancy			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Use of Nottingham grading system (Elston & Ellis 1991) for all types of invasive breast cancer (incl. status post neoadjuvant systemic therapy) 	5	D	++
<ul style="list-style-type: none"> In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used 	5	D	++
<ul style="list-style-type: none"> Grading of DCIS, e.g. according to WHO-Classification, (5th ed., 2019) 	5	D	++
<ul style="list-style-type: none"> Reporting of tumor grade in numeric form (e.g. G3) 	5	D	++

Grading

1. Elston C, Ellis I. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*. 1991;19(5):403-41
2. WHO. Breast Tumours: WHO Classification of Tumours. 5 ed. Lyon (France): International Agency for Research on Cancer; 2019
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4. Chang JM, McCullough AE, Dueck AC, et al. Back to Basics: Traditional Nottingham Grade Mitotic Counts Alone are Significant in Predicting Survival in Invasive Breast Carcinoma. *Ann Surg Oncol*. 2015;22 Suppl 3:S509-S515. doi:10.1245/s10434-015-4616-y.
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6. Rakha EA, Reis-Filho JS, Baehner F, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. *Breast Cancer Res*. 2010;12(4):207. doi:10.1186/bcr2607.

7. Rakha EA, El-Sayed ME, Lee AHS, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. *J Clin Oncol*. 2008;26(19):3153-3158. doi:10.1200/JCO.2007.15.5986.

Grading of invasive lobular carcinoma

1. Rakha EA, El-Sayed ME, Menon S, Green AR, Lee AHS, Ellis IO. Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. *Breast Cancer Res Treat*. 2008;111(1):121-127. doi:10.1007/s10549-007-9768-4.
2. Talman M-LM, Jensen M-B, Rank F. Invasive lobular breast cancer. Prognostic significance of histological malignancy grading. *Acta Oncol*. 2007;46(6):803-809. doi:10.1080/02841860601137397.
3. Bane AL, Tjan S, Parkes RK, Andrulis I, O'Malley FP. Invasive lobular carcinoma: to grade or not to grade. *Mod Pathol*. 2005;18(5.

Reporting: Tumor Size and Total Extent of Tumor			
	Oxford		
	LoE	GR	AGO
▪ Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results	5	D	++
▪ Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality	5	D	++
▪ Reporting of size of non-invasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2 x invasive Ca)	5	D	++

Determination of tumor size

1. Pritt, B., Tessitore, J. J., Weaver, D. L. et al (2005). The effect of tissue fixation and processing on breast cancer size. Human Pathology, 36(7), 756–760.
2. Varma, S., Ozerdem, U., & Hoda, S. A. (2014). Complexities and challenges in the pathologic assessment of size (T) of invasive breast carcinoma. Advances in Anatomic Pathology, 21(6), 420–432.


Multifocality

1. Hilton, J. F., Bouganim, N., Dong, B., et al. (2013). Do alternative methods of measuring tumor size, including consideration of multicentric/multifocal disease, enhance prognostic information beyond TNM staging in women with early stage breast cancer: an analysis of the NCIC CTG MA.5 and MA.12 clinical trials. Breast Cancer Research and Treatment, 142(1), 143–151.
2. NHS (2005) Pathology Reporting of Breast Disease. IA Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology
<http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58-low-resolution.pdf>
3. Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. Annals of Oncology. 2008 Apr 1;19(4):614–22.

4. Tot, T., Gere, M., Pekár, G., et al. (2011). Breast cancer multifocality, disease extent, and survival. *Human Pathology*, 42(11), 1761–1769.

Extensive intraductal component (EIC)

1. Mai, K. T., Perkins, D. G., & Mirsky, D. (2003). Location and extent of positive resection margins and ductal carcinoma in situ in lumpectomy specimens of ductal breast carcinoma examined with a microscopic three-dimensional view. *The Breast Journal*, 9(1), 33–38.
2. Smitt, M. C., Nowels, K., Carlson, R. W., et al. (2003). Predictors of reexcision findings and recurrence after breast conservation. *International Journal of Radiation OncologyBiologyPhysics*, 57(4), 979–985
3. Schnitt, S. J., Connolly, J. L., Khettry, U., et al. (1987). Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. *Cancer*, 59(4), 675–681.
4. Sinn, H. P., Anton, H. W., Magener, A., et al. (1998). Extensive and predominant in situ component in breast carcinoma: their influence on treatment results after breast-conserving therapy. *European Journal of Cancer*, 34(5), 646–653



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Reporting: pTNM

Oxford		
LoE	GR	AGO
5	D	++

- **Use of current UICC classification (8th ed.)**
- pT 1-3:** Invasive tumor size (largest focus in case of multifocality or multicentricity)
- pT4:** Invasion of dermis alone does not qualify as pT4. Criteria for pT4a/b/c/d must be met.
- pT4d:** Negative skin biopsy does not rule out pT4d (inflammatory carcinoma).
- pM:** pM1 indicates any non-regional disease, except 2nd primary contralateral. Use of MX is not recommended.

TNM staging (7th ed.) according to UICC und AJCC

1. Wittekind C. *TNM - Klassifikation Maligner Tumoren 8. Aufl.* John Wiley & Sons; 2016.
2. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours 8th ed.* John Wiley & Sons; 2016.
3. American-Joint-Committee-on-Cancer (2017) AJCC cancer staging manual 8th ed. Springer, New York; London
4. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-99. doi:10.3322/caac.21388.

pT4b category: Involvement of the skin

1. Wieland, A., Louwman, M., Voogd, A., et al. (2004). Determinants of prognosis in breast cancer patients with tumor involvement of the skin (pT4b). *The Breast Journal*, 10(2), 123–128. doi:21279 [pii]
2. Harms, K., & Wittekind, C. (2009). Prognosis of women with pT4b breast cancer: the significance of this category in the TNM system. *European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*, 35(1), 38–42. doi:10.1016/j.ejso.2007.11.016

pT4d category: Inflammatory breast cancer

1. Yamauchi, H., Woodward, W. A., Valero, V., et al. (2012). Inflammatory breast cancer: what we know and what we need to learn. *The Oncologist*, 17(7), 891–899. doi:10.1634/theoncologist.2012-0039

Reporting: Margins of Resection and R-Classification			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm) 	5	D	++
<ul style="list-style-type: none"> Reporting of minimal distance to resection margin and its topography 	5	D	++
<ul style="list-style-type: none"> R-Classification 	5	D	++
R0: No residual tumor			
R1: Microscopic invasive or noninvasive carcinoma involving resection margin			
RX: Presence of residual tumor cannot be assessed (e.g. tumor in multiple specimens)			

Pathological margin assessment

1. Schnitt, S. J., Moran, M. S., Houssami, N., et al. (2014). The 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: Perspectives for Pathologists. Archives of Pathology & Laboratory Medicine. doi:10.5858/arpa.2014-0384-ED
2. Houssami, N., & Morrow, M. (2014). Margins in breast conservation: a clinician's perspective and what the literature tells us. Journal of Surgical Oncology, 110(1), 2–7. doi:10.1002/jso.23594
3. Houssami, N., Macaskill, P., Marinovich, M. L., et al. (2014). The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Annals of Surgical Oncology, 21(3), 717–730.
4. Yeap, B. H., Muniandy, S., Lee, S.-K., et al. (2007). Specimen shrinkage and its influence on margin assessment in breast cancer. Asian Journal of Surgery / Asian Surgical Association, 30(3), 183–187. doi:10.1016/S1015-9584(08)60020-2
5. Dooley, W. C., & Parker, J. (2005). Understanding the mechanisms creating false positive lumpectomy margins. American Journal of Surgery, 190(4), 606–608. doi:10.1016/j.amjsurg.2005.06.023
6. Keskek, M., Kothari, M., Ardehali, B. et al. (2004). Factors predisposing to cavity margin positivity following conservation surgery for breast cancer. European Journal of Surgical Oncology, 30(10), 1058–1064. doi:10.1016/j.ejso.2004.07.019
7. Graham, R. A., Homer, M. J., Katz, J., et al. (2002). The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer. American Journal of Surgery, 184(2), 89–93.

R-Classifikation

1. Wittekind C, Compton C, Quirke P, et al. A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. *Cancer*. 2009;115(15):3483-3488. doi:10.1002/cncr.24320.

Reporting: Lymphovascular Invasion			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ L1: Lymphovascular invasion ▪ L0: No lymphovascular invasion 	5	D	++
<ul style="list-style-type: none"> ▪ IHC for evaluation of lymphovascular invasion 	3b	C	-
<ul style="list-style-type: none"> ▪ Differentiation of peritumoral and extensive lymphovascular invasion 	3b	C	++
<ul style="list-style-type: none"> ▪ Reporting of venous invasion (V0/V1) optional, prognostic significance not established 	5	D	+

Definition of L- and V-Classification


1. Wittekind C. *TNM - Klassifikation Maligner Tumoren 8. Aufl.* John Wiley & Sons; 2016.

Detection of angioinvasion

1. Manfrin, E., Remo, A., Pancione, M. et al. (2014). Comparison between invasive breast cancer with extensive peritumoral vascular invasion and inflammatory breast carcinoma: a clinicopathologic study of 161 cases. *American Journal of Clinical Pathology*, 142(3), 299–306. doi:10.1309/AJCPOXKX67KRAOVM
2. Ren, S., Abuel-Haija, M., Khurana, J. S., et al. (2011). D2-40: an additional marker for myoepithelial cells of breast and the precaution in interpreting tumor lymphovascular invasion. *International Journal of Clinical and Experimental Pathology*, 4(2), 175–182.
3. Van den Eynden, G. G., Van der Auwera, I., Van Laere, S. et al. (2006). Distinguishing blood and lymph vessel invasion in breast cancer: a prospective immunohistochemical study. *British Journal of Cancer*, 94(11), 1643–1649.
4. Zaorsky, N. G., Patil, N., Freedman, G. M., et al. (2012). Differentiating lymphovascular invasion from retraction artifact on histological specimen of breast carcinoma and their implications on prognosis. *Journal of Breast Cancer*, 15(4), 478–480.

Prognostic significance of lymphovascular invasion

1. Gujam, F. J. A., Going, J. J., Edwards, J. et al. (2014). The role of lymphatic and blood vessel invasion in predicting survival and methods of detection in patients with primary operable breast cancer. *Critical Reviews in Oncology/Hematology*, 89(2), 231–241. doi:10.1016/j.critrevonc.2013.08.014
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Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

- **Identification of tumors with predominant lymphocytic infiltrate (> 50 %) in tumor stroma (according to Salgado et al.*)**

Consider only lymphocytic infiltrate in tumor stroma and not at the invasion front

Do not consider central fibrosis and necrotic areas

Report average of lymphocytic infiltrate as percentage

Oxford		
LoE	GR	AGO
5	D	+/-

* Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Annals of Oncology*

Definition and impact of predominant lymphocytic infiltration

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Reporting: Evaluation after Neoadjuvant Chemotherapy			
	Oxford		
	LoE	GR	AGO
▪ Identification of tumor bed, otherwise ypTX	4	D	++
▪ Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma	4	D	++
▪ pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded	2b	D	+
▪ Use of IHC to identify tumor residues (lymphnodes)	2b	B	+/-
▪ Reporting of ypTN after neoadjuvant systemic therapy	5	D	++
▪ Repeat IHC for ER, PR, and HER2	5	D	+/-
▪ Intraoperative frozen section (reduced sensitivity)	5	D	-
▪ Tumorregression-Scores: RCB-Score or Sataloff-Score	4	D	+/-

Specimen processing after neoadjuvant chemotherapy


1. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol*. 2015;28(9):1185-1201. doi:10.1038/modpathol.2015.74
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RCB-Score

1. RCB-Calculator: <http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert>
2. Bossuyt V, Symmans WF. Standardizing of Pathology in Patients Receiving Neoadjuvant Chemotherapy. *Ann Surg Oncol*. 2016;23(10):3153-3161. doi:10.1245/s10434-016-5317-x
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Sataloff-Score

1. Sataloff DM, Mason BA, Prestipino AJ, et al. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg*. 1995;180(3):297-306.

Special Studies: ER-Testing by IHC		Oxford		
		LoE	GR	AGO
 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2022.1E</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p>	<ul style="list-style-type: none"> Immunohistochemical detection on paraffin embedded (FFPE) tissue Reporting percentage of pos. tumor nuclei (pos. if $\geq 10\%$, low pos. if $\geq 1\%$–10%) Staining intensity Only Allred Score (0–8) or Remmele Score (0–12) Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy 	1a	A	++
		1a	A	++
		4	D	+
		4	D	-
		5	D	+

ASCO/CAP Guideline for ER- and PR-testing

1. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol*. 2020;38(12):JCO1902309–1366. doi:10.1200/JCO.19.02309
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IHC-testing for ER-positivity

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in Breast Cancer by Immunohistochemistry. Journal of the National Comprehensive Cancer Network, 7 Suppl 6, S1–S21– quiz S22–3. Retrieved from http://www.nccn.org/JNCCN/PDF/2009_estrogen_receptor_and_progesterone_receptor_immunohistochemistry.pdf

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IHC Scores

1. Allred, D. C., Harvey, J. M., Berardo, M., et al. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Modern Pathology*, 11(2), 155–168.
2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) für den immunhistochemischen Östrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. *Der Pathologe*, 8(3), 138–140.

Monoclonal Antibodies for ER-Testing

1. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. *J Clin Oncol*. 2006 Dec 20;24(36):5637-44.

	<h2 style="color: green; text-align: center;">Low ER+ (1–10 %)</h2>		
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	<p>Sanford, R. A. <i>et al.</i> <i>Cancer</i> 121, 3422–3427 (2015). DOI: 10.1002/cncr.29572</p>	<p>314 Pat. 1–9% ER, Anteil BRCA mutierter Fälle wie bei ER -</p>	<p>High Incidence of Germline BRCA Mutation in Patients with ER Low-Positive / PR Low-Positive / HER-2 neu Negative Tumors</p>
	<p>Deyarmin, B. <i>et al.</i> <i>Ann Surg Oncol</i> 20, 87–93 (2013). DOI: 10.1245/s10434-012-2588-8</p>	<p>26 Pat. 1–10% ER, Genexpression eher wie TN oder HER2 enr</p>	<p>Effect of ASCO / CAP Guidelines for Determining ER Status on Molecular Subtype</p>
	<p>Prabhu, J. S. <i>et al.</i> <i>J Cancer</i> 5, 156–165 (2014) DOI: 10.7150/jca.7668</p>	<p>21 Pat. 1–10% ER, Genexpression wie ER-, Überleben < ER+</p>	<p>A Majority of Low (1–10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors</p>
	<p>Yi, M. <i>et al.</i> <i>Annals of Oncology</i> 25, 1004–1011 (2014). DOI: 10.1093/annonc/mdu053</p>	<p>251 Pat. 1–9% ER Überleben = ER-</p>	<p>Which threshold for ER positivity? A retrospective study based on 9639 patients</p>


Low ER+ Group

1. Dieci, M. V. *et al.* Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. *Npj Breast Cancer* **7**, 101 (2021).
2. Villegas, S. L. *et al.* Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors – An analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer* **148**, 159–170 (2021).
3. Poon, I. K. *et al.* The significance of highlighting the oestrogen receptor low category in breast cancer. *British Journal of Cancer* **123**, 1223–1227 (2020).
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- 1, S61–S63 (2017).
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10. Nordenskjöld, A. *et al.* Progesterone receptor positivity is a predictor of long-term benefit from adjuvant tamoxifen treatment of estrogen receptor positive breast cancer. *Breast Cancer Research and Treatment* 160, 313–322 (2016).
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15. Yi, M. *et al.* Which threshold for ER positivity? a retrospective study based on 9639 patients. *Annals of Oncology* 25, 1004–1011 (2014).
16. Deyarmin, B. *et al.* Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. *Annals of Surgical Oncology* 20, 87–93 (2013).
17. Reisenbichler, E. S. *et al.* Interobserver concordance in implementing the 2010 ASCO/CAP recommendations for reporting ER in breast carcinomas: a demonstration of the difficulties of consistently reporting low levels of ER expression by manual quantification. *American journal of clinical pathology* 140, 487–494 (2013).
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19. Rakha, E. A. *et al.* Low-estrogen receptor-positive breast cancer: the impact of tissue sampling, choice of antibody, and molecular subtyping. *Journal of Clinical Oncology* 30, 2929-30-author reply 2931 (2012).
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25. Viale, G. *et al.* Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG 1-98. *Journal of Clinical Oncology* 25, 3846–3852 (2007).
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27. EBCTCG, Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 365, 1687–1717 (2005).



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Special Studies: PR-Testing by IHC

Oxford		
LoE	GR	AGO
1a	A	++
1a	A	++
4	D	-

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
- Reporting percentage of pos. tumor nuclei (pos. if ≥ 10 %)
- Only Allred Score (0 - 8) or Remmele Score (0 - 12)

IHC-testing for PR-positivity

1. Allred, D. C. (2010). Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. *Modern Pathology*, 23 Suppl 2, S52–9. doi:10.1038/modpathol.2010.55
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Prognostic significance

1. Braun, L., Mietzsch, F., Seibold, P., et al. (2013). Intrinsic breast cancer subtypes defined by estrogen receptor signalling - prognostic relevance of progesterone receptor loss, 26(9), 1161–1171.
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Aberrant Expression of ER in triple negative breast cancer

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IHC Scores

1. Allred, D. C., Harvey, J. M., Berardo, M., et al. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Modern Pathology, 11(2), 155–168.
2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) für den immunhistochemischen Östrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.



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Additional Special Studies: Molecular Analysis of ER / PR Status

	Oxford	
	LoE	GR
■ Evaluation of hormone receptors using validated gene expression test kits	3b	A
■ Exclusive evaluation of hormone receptor by RNA-quantification	5	D
■ Use of molecular receptor analysis for subtyping	3b	A

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Clinical significance of mRNA expression of ESR-alpha, PgR and concordance with IHC results

1. Dixon JM, Cameron DA, Arthur LM, et al. Accurate Estrogen Receptor Quantification in Patients with Negative and Low-Positive Estrogen-Receptor-Expressing Breast Tumors: Sub-Analyses of Data from Two Clinical Studies. *Adv Ther.* 2019;378(suppl 6):771-841. doi:10.1007/s12325-019-0896-0.
2. Chapman J-AW, Sgroi DC, Goss PE, et al. Relapse-free survival of statistically standardized continuous RT-PCR estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2): NCIC CTG MA.14. *Breast Cancer Res Treat.* 2016;157(1):101-108. doi:10.1007/s10549-016-3806-z.
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4. Viale G, Slaets L, Bogaerts J, et al. High concordance of protein (by IHC), gene (by FISH; HER2 only), and microarray readout (by TargetPrint) of ER, PgR, and HER2: results from the EORTC 10041/BIG 03-04 MINDACT trial. *Ann Oncol.* 2014;25(4):816-823. doi:10.1093/annonc/mdu026.
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negative/progesterone receptor-positive breast cancers. *Breast Cancer Res Treat*. 2014;143(2):403-409. doi:10.1007/s10549-013-2763-z.

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8. Denkert C, Loibl S, Kronenwett R, et al. RNA-based determination of ESR1 and HER2 expression and response to neoadjuvant chemotherapy. *Ann Oncol*. 2013;24(3):632-639. doi:10.1093/annonc/mds339.
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HER2-Analysis by IHC

	Oxford LoE	GR	AGO
<ul style="list-style-type: none"> ■ Reporting of immunohistochemistry (IHC): ■ 3+ staining pattern: HER2+ if strong complete circular membrane staining of > 10 % invasive cells ■ 2+ staining pattern: If > 10 % circular but moderate / weak membrane staining or ≤ 10 % strong staining, U-shaped staining in micropapillary carcinoma: ISH required (CISH, SISH, FISH) 	1a	A	++
	1a	A	++


ASCO/CAP Guideline on HER2-Testing

1. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med*. May 2018;arpa.2018–0902–SA. doi:10.5858/arpa.2018-0902-SA.

IHC and molecular HER2-Testing

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HER2-Analysis by ISH when IHC 2+

- **Single-Color In-Situ-Hybridisation (ISH):**
 - HER2+ if signal counts ≥ 6 in at least 20 cohesive cells
 - negative if signal counts < 4 signals/nucleus
 - 2-Color ISH recommended for ≥ 4 and < 6 signals/nucleus
- **Two-Color In-Situ-Hybridisation (ISH):**
 - Group 1: Ratio ≥ 2.0 and signals/nucleus $\geq 4.0 \rightarrow$ HER2+
 - Group 2: Ratio ≥ 2.0 and signals/nucleus $< 4.0 \rightarrow$ HER2- (no benefit of anti-HER2 therapy)
 - Group 3: Ratio < 2.0 and signals/nucleus $\geq 6.0 \rightarrow$ HER2+ (but benefit of anti-HER2 therapy not certain)
 - Group 4: Ratio < 2.0 and signals/nucleus ≥ 4.0 und $< 6 \rightarrow$ HER2- (no benefit of anti-HER2 therapy)
 - Group 5: Ratio < 2.0 und signals/nucleus $< 4.0 \rightarrow$ HER2-

Oxford		
LoE	GR	AGO
3a	C	++
3a	D	++

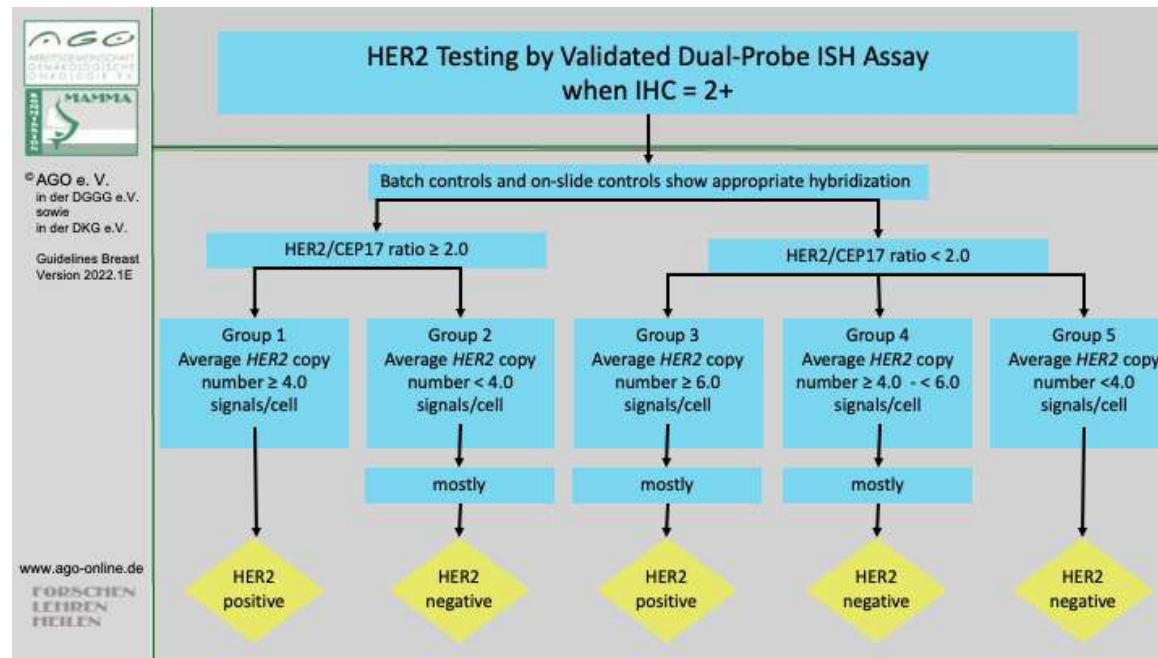
ASCO/CAP Guideline on HER2-Testing

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ISH HER2-Testing

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ASCO/CAP Guideline on HER2-Testing

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HER2 Testing on Core Biopsies

False positive immunohistochemical labeling may occur in core biopsies. Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium.

Alternatively, all G1 and G2 cases with HER2 3+ in core biopsies may be analyzed by ISH or may be re-evaluated in the resection specimen.

False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and PR positive, Tubular (at least 90 % pure), Mucinous (at least 90 % pure) Cribriform (at least 90 % pure), Adenoid cystic carcinoma (90 % pure).

In case of discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method. If still discrepancy – anti-HER2-treatment if amplified in one of both samples. Expected rate of HER2-overexpression: 15 % HER2 positive.

ASCO/CAP Guideline on HER2-Testing

1. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med*. May 2018;arpa.2018–0902–SA. doi:10.5858/arpa.2018-0902-SA.

Additional Special Studies: Molecular Analysis of HER2 Status			
	Oxford		
	LoE	GR	AGO
▪ Therapy decisions should only be based on IHC and ISH	1a	A	++
▪ Evaluation of HER2 using validated gene expression test kits	3b	B	-
▪ Evaluation of HER2-amplification by RNA-sequencing	5	D	-
▪ Use of molecular HER2-testing for subtyping	3b	B	+/-

Genomic and gene expression analysis of HER2

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Special Studies: Evaluation of Ki-67 Score			
	Oxford		
	LoE	GR	AGO
▪ Counting of tumor nuclei at the invasion front	5	D	++
▪ Semiquantitative eyeballing or counting of labelled cells in core needle biopsies	2	A	++
▪ Consideration of weakly stained tumor nuclei	5	D	++
▪ Reporting of Ki-67 positive nuclei as percentage	5	D	++
▪ Establishing of laboratory standards and cut-off values	5	D	++
▪ Use of image analysis for objective Ki-67 evaluation	5	D	+
▪ Determination of Ki-67 dynamics after short term (2-4 weeks) endocrine therapy*	1b	B	+

* See chapter Neoadjuvant Systemic Therapy

Ki-67 Methods and Reproducibility

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Impact of Ki-67 staining

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Ki67 als dynamischer Marker nach Kurzzeit endokriner Therapie

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Reproducibility – Quality Assurance is Key for Clinical Decision Making

- **ER / PR: concordance central vs local is high (97 %; Plan B, SABCS 2014)**
- **Grade: concordance central vs local is 68 % (PlanB, JCO 2016)**
- **HER2: frequency of false-positive test results 6 % (ASCO /CAP JCO 2013)**
- **Impact of routine pathologic review in N0 BC: 20 % changes: grade 40 %, LVI 26 %, N 15 %, margin 12 % (JCO 2012)**
- **pN0 from MIRROR study: pN0 was upstaged in 22 %, in central pathology review (Ann Oncol 2012)**
- **Ki-67:**
 - **Inter- and intraobserver variability in measurement of Ki-67 is high (J Nat. Cancer Institute 2011)**
 - **High reproducibility for low and high Ki-67 levels (J Pathol 2002)**
 - **Standardized methodology improves analytical validity (JNCI 2020)**

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Predictive PD-L1 Assay

Immunohistochemical assay

Immune Score (IC): Cytoplasmic staining of at least 1 % of the leucocyte stromal infiltrate (lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses) for prediction of atezolizumab efficacy in triple-negative metastatic breast cancer.

Metastatic or primary tumor tissue

Detection with antibodies equivalent to Impassion 130 study reagents

Combined positive score (CPS): positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100 (≥ 10 = positive) for prediction of pembrolizumab efficacy in metastatic triple-negative breast cancer.

Oxford

LoE GR AGO

2 A ++


2 A ++

3 B +

2 A ++

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 Mutation Diagnostics* in mBC: „Precision Medicine“ for Targeted Therapies							
Altered genes	Therapeutic relevance	Gene region	Material	Oxford			
				LOE	GR	AGO	
BRCA1, BRCA2	PARP-Inhibitors	All exons	Germline: Blood cells	1b	A	++	
			Somatic: Tissue	2b	B	+/-	
PALB2	PARP-Inhibitors	Exons 7,9 and 20	Germline: Blood cells	2b	B	+	
PIK3CA	Alpelisib		Primary tumor, metastases, plasma	1b	A	++	
HER2-mutation (independent of HER2-status)	Neratinib, lapatinib	Kinase- and extracellular domains; S310, L755, V777, Y772_A775dup	Primary tumor, metastases, plasma particul. lobular BC	4	C	+/-	
ESR1	Resistance against AI	Exons 4,7 und 8	Metastases, plasma	2b	B	+/-	
NTRK gene fusion	Larotrectinib, entrectinib	Fusion- and splice variants	Tumor tissue, particul. secretory breast cancer	2a	B	+	
MSI	Pembrolizumab	Microsatellite-instability	Tissue	2a	B	+	
* Ideally panel diagnostics							

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