



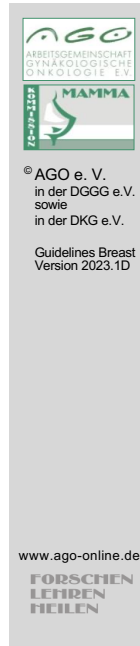
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Guidelines Breast  
Version 2023.1D

FORSCHEN  
LEHREN  
HEILEN

# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Pathologie



## Pathologie

- **Versionen 2004–2022:**  
Blohmer / Costa / Fehm / Friedrichs / Harbeck / Huober /  
Kreipe / Lück / Maass / Schneeweiss/ Sinn / Thomssen / Schmidt
- **Version 2023:**  
Kreipe / Schmidt / Sinn

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](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](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](https://sgpath.ch/docs/QRL/QRL_SGPath_Mamma_2017.pdf)

## Präanalyse: Fixation

	Oxford		
	LoE	GR	AGO
▪ Minimierung der Zeit bis zur Fixation (kalte Ischämiezeit)	5	D	++
▪ Einhaltung einer minimalen Fixationszeit von 6 Stunden zur Gewährleistung einer optimalen Antigenerhaltung	5	D	++
▪ Optimale Fixationszeit bei Stanzbiopsien: 6–72 h	5	D	++
▪ Optimale Fixationszeit bei Resektaten: 12–72 h	5	D	++
▪ Verwendung neutral gepufferter Formalinlösung	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.

## Indikationen der Mamma-Zytologie\*

- Mamillensekret
- Tumor\*
- Zyste
- Lymphknoten

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

\* Ultraschall gesteuerte Stanzbiopsie empfohlen

- 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.
- 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.
- 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.
- 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.
- He, X., Wang, Y., Nam, G., Lourenco, A. P. 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>
- 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>
- 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>

## Aufarbeitung: Stanzbiopsien (Ultraschall gesteuert / stereotaktisch)

	Oxford		
	LoE	GR	AGO
▪ <b>Aufarbeitung in Schnittstufen</b> (14G: 1 – 3 Stufen / 11G, 8G: 6 – 8 Stufen)	5	D	++
▪ <b>Radiologisch-pathologische Korrelation (Mikrokalk / Dichte), Anwendung der B-Klassifikation</b>	1b	B	++
▪ <b>Schnellschnittdiagnostik an Stanzbiopsien</b>	5	D	--
▪ <b>Evaluation des ER/PR und HER2-Status</b>	3b	C	++
▪ <b>Umlaufzeit &lt; 24 h (Dignität)</b>	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

## Aufarbeitung: Brusterhaltende Therapie

	Oxford		
	LoE	GR	AGO
■ Die Lamellierung erfolgt senkrecht zur Längsachse (bzw. bei kugeligen Exzidaten senkrecht zur Mamillen-Peripherie-Achse)	5	D	++
■ Systematisches Sampling, mindestens ein Gewebeblock pro cm Resektat	5	D	++
■ Tuschemarkierung der Resektionsränder	5	D	++
■ Makroskopische Dokumentation der Gewebescheiben durch Präparateradiographie, Photodokumentation oder Diagramm	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](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.

## Aufarbeitung: Mastektomie

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Sampling der Resektionsränder</b> <ul style="list-style-type: none"> <li>■ Hautränder tumornah</li> <li>■ dorsaler Rand</li> <li>■ weitere Ränder, wenn knapp (&lt; 1 cm)</li> </ul> </li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>■ <b>Beachtung der Weichgewebsränder bei hautsparender Mastektomie</b></li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>■ <b>Sampling von nicht involvierten Quadranten, Haut über Tumor, Mamille und retroareoläre Region</b></li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>■ <b>Systematische Probenentnahme bei prophylaktischer Mastektomie (BRCA-1/2 pos. Patienten)</b></li> </ul>	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](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.

## Aufarbeitung: Sentinel-Lymphknoten

	Oxford		
	LoE	GR	AGO
▪ <b>Vollständige Aufarbeitung am Paraffinschnitt mit Schnittstufen von <math>\leq 500</math> <math>\mu\text{m}</math></b>	5	D	++
▪ <b>Zytokeratin-Immunhistologie</b>			
▪ zum Nachweis von Mikrometastasen, wenn suspekt	2b	B	+
▪ zum Nachweis von Mikrometastasen nach NACT	2b	B	+
▪ routinemäßig	5	D	+/-
▪ <b>Schnellschnittuntersuchung</b> (anschließender Paraffinschnitt erschwert)			
▪ bei klinischer Konsequenz	5	D	+
▪ bei nicht zu erwartender Konsequenz	5	D	-
▪ <b>Abtupfzytologie anstatt oder zusätzlich zur Schnellschnittuntersuchung</b>	3b	C	+/-
▪ <b>RT-PCR zum Nachweis von Metastasen</b>	4	D	-
▪ OSNA	3b	B	-

### Statement: Evaluation of sentinel node biopsy

1. 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>
2. 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

1. 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

1. 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>





Statement: Lesions  $\geq 1$  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.


## Befundung: Histologischer Tumortyp

Oxford		
LoE	GR	AGO
3b	C	++

- **Histologischer Tumortyp entsprechend WHO-Klassifikation (5. Aufl. 2019)**
  - **Partielle spezielle Differenzierung:**  
> 50% NST-Komponente  
und < 50% spezieller Tumortyp (Minorkomponente)
  - **Gemischte Differenzierung:**  
> 50% spezieller Tumortyp  
und < 50% NST-Komponente  
Beispiel: Muzinöses MaCa, Mischtyp
  - **Reine Typen:**  
> 90% des Tumors vom speziellen Typ  
Beispiel: tubuläres oder kribriiformes Ca.


### 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.
3. Tan, P. H., & Ellis, I. O. (2013). Myoepithelial and epithelial-myoepithelial, mesenchymal and fibroepithelial breast lesions: updates from the WHO Classification of Tumours of the Breast 2012. *Journal of Clinical Pathology*, 66(6), 465–470. doi:10.1136/jclinpath-2012-201078
4. Viale, G. (2012). The current state of breast cancer classification. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 23 Suppl 10(suppl 10), x207–x210. doi:10.1093/annonc/mds326

 <p>© AGO e. V. in der DGOG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	<b>Ductal TNBC: Comparable survival rates and similar response rates to chemotherapy for ER = 0% compared to ER 1% - &lt;10%</b>		
	Reference	Patients	Results
	Villegas, S. L. <i>Eur J Cancer</i> <b>148</b> , 159–170 (2021) DOI: 10.1016/j.ejca.2021.02.020	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.	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.
	Dieci, M. V. et al. <i>Npj Breast Cancer</i> <b>7</b> , 101 (2021) 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).	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).
	Reddy, S. M. et al. <i>British Journal of Cancer</i> <b>118</b> , 17–23 (2018) DOI: 10.1038/bjc.2017.379	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.	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.

### 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/adjvant 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>  <b>Apocrine TNBC: More favorable survival and poor response to adjuvant chemotherapy</b> </div>			
<div> <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p> </div>	Reference	Patients	Results
	Saridakis, A. <i>et al.</i> <i>Ann Surg Oncol</i> <b>28</b> , 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> <b>53</b> , 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> <b>40</b> , 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

1. Saridakis, A. *et al.* Apocrine Breast Cancer: Unique Features of a Predominantly Triple-Negative Breast Cancer. *Ann Surg Oncol* **28**, 5610–5616 (2021).
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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).



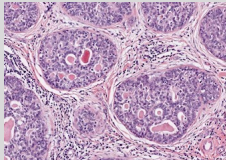
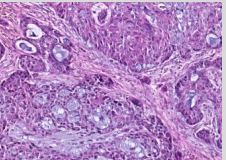
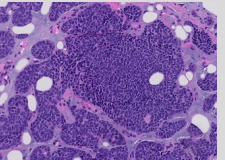
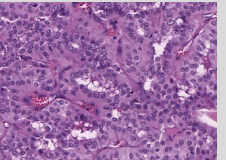
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## Rare and salivary-type TNBC: Tumors with divergent clinical behavior and specific genetic alterations

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

### 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).
3. Foschini, M. P. et al. Solid Variant of Adenoid Cystic Carcinoma of the Breast: A Case Series With Proposal of a New Grading System. *International Journal of Surgical Pathology* **24**, 97–102 (2016).
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### 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).
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5. Cabello, C. et al. Case report and review of the literature: secretory breast cancer in a 13-year-old boy--10 years of follow up. *Breast*

(2017).

6. Alsadoun, N. *et al.* Solid papillary carcinoma with reverse polarity of the breast harbors specific morphologic, immunohistochemical and molecular profile in comparison with other benign or malignant papillary lesions of the breast: a comparative study of 9 additional cases. *Modern Pathology* **31**, 1367–1380 (2018).
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  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).
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1. 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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  3. 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).
  4. Asioli, S. *et al.* Polymorphous adenocarcinoma of the breast. Report of three cases. *Virchows Arch* **448**, 29–34 (2006).



## Befundung: Differenzierungsgrad

	Oxford		
	LoE	GR	AGO
▪ Anwendung des Nottingham-Grading (Elston & Ellis 1991) für alle Typen des invasiven Mammakarzinoms (auch nach neoadj. Therapie)	5	D	++
▪ Bei sehr wenig Tumorgewebe rein nukleäres Grading oder Heranziehung zusätzlicher Kriterien wie Ki-67 Proliferationsfraktion	5	D	++
▪ Grading des DCIS z.B. gemäß WHO-Klassifikation des Mammakarzinoms (5. Aufl., 2019)	5	D	++
▪ Wiedergabe des Tumorgrading zumindest auch numerisch (z.B. 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
3. Christgen M, Länger F, Kreipe H. Histologisches Grading beim Mammakarzinom. *Der Pathologe*. 2016;37(4):328-336. doi:10.1007/s00292-016-0182-8.
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.
5. Schwartz AM, Henson DE, Chen D, Rajamarthandan S. Histologic grade remains a prognostic factor for breast cancer regardless of the number of positive lymph nodes and tumor size: a study of 161 708 cases of breast cancer from the SEER Program. *Arch Pathol Lab Med*. 2014;138(8):1048-1052. doi:10.5858/arpa.2013-0435-OA.
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).

## Befundung: Tumorgröße und gesamte Tumorausdehnung

	Oxford		
	LoE	GR	AGO
■ Invasive Tumorgröße, unter Berücksichtigung des makroskopischen und histologischen Befundes und klinisch-bildgebender Befunde	5	D	++
■ Bei Satellitenherden und Multifokalität zusätzlich Gesamtausdehnung des invasiven Karzinoms	5	D	++
■ Angabe der Ausdehnung der DCIS- oder LCIS-Komponente, wenn extensiv (mehr als das Doppelte der Ausdehnung des invasiven Karzinoms)	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.
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#### 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

## Befundung: pTNM

Oxford		
LoE	GR	AGO
5	D	++

### ■ Anwendung der aktuellen UICC-Klassifikation (8. Auflage)

- pT1–3:** Größter invasiver Tumorherd, nicht Gesamt-ausdehnung, Multifokalität od. Multizentrität
- pT4:** Alleinige Infiltration der Dermis nicht ausreichend. Kriterien für pT4a/b/c/d müssen erfüllt sein
- pT4d:** Eine negative Hautbiopsie schließt pT4d (inflammatorisches Karzinom) nicht aus
- pM:** pM1 bei jeglichem nicht regionärem Tumornachweis, ausgenommen kontralateralem Zweitkarzinom. Eine Angabe von MX od. pMX wird nicht empfohlen.

### 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 8<sup>th</sup> 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

## Befundung: Beurteilung der Resektionsränder, R-Klassifikation

	Oxford		
	LoE	GR	AGO
▪ Randsituation, makroskopisch Abstand zu allen Rändern und histologisch die nächsten < 1cm untersuchen	5	D	++
▪ Angabe des minimalen histologischen Sicherheitsabstandes und dessen Topographie	5	D	++
▪ R-Klassifikation	5	D	++
<b>R0: Kein Residualtumor</b>			
<b>R1: Histologisch invasives oder nicht invasives Karzinom im Resektionsrand</b>			
<b>RX: Beurteilung des Resektionsrandes nicht möglich (z.B. Tumor in mehreren Teilpräparaten)</b>			

### 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.



## Befundung: Lymphgefäßinvasion

- **L1: Nachweis einer Lymphgefäßinvasion**  
**L0: Keine eindeutige Lymphgefäßinvasion**
- **IHC zum Nachweis einer Lymphgefäßinvasion**
- **Unterscheide: peritumorale und ausgedehnte Lymphgefäßinvasion**
- **Angabe der Blutgefäßinvasion (V0/V1) fakultativ, da prognostische Relevanz unklar**

Oxford		
LoE	GR	AGO
5	D	++
3b	C	-
3b	C	++
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
2. Colleoni, M., Rotmensz, N., Maisonneuve, P., et al. (2007). Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. *Annals of Oncology*, 18(10), 1632–1640
3. Rakha, E. A., Martin, S., Lee, A. H. S., et al. (2011). The prognostic significance of lymphovascular invasion in invasive breast carcinoma. *Cancer*, 118(15), 3670–3680.

## Befundung: Evaluation tumor-infiltrierender Lymphozyten (TIL)

Oxford		
LoE	GR	AGO
5	D	+/-

- Identifikation von Tumoren mit prädominantes lymphozytären Infiltrat (> 50%) im Tumorstroma (n. Salgado et al.\*)

Nur das intratumorale Infiltrat im Stroma und nicht an der Invasionsfront berücksichtigen

Zentrale Fibrose- und Nekrosezonen nicht bewerten

Durchschnittswert des lymphozytären Infiltrates in Prozent angeben

- \* 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*

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1. Kos Z, Roblin E, Kim RS, et al. Pitfalls in assessing stromal tumor infiltrating lymphocytes (sTILs) in breast cancer. *npj Breast Cancer*. 2020;6(1):17–16. doi:10.1038/s41523-020-0156-0.
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## Befundung: nach neoadjuvanter Chemotherapie

	Oxford		
	LoE	GR	AGO
▪ Identifikation des Tumorbetts, sonst ypTX	4	D	++
▪ Angabe der Tumorgroße als max. Tumorbettgröße mit vitalem, invasiven Ca.	4	D	++
▪ pCR definiert als Fehlen invasiven Karzinoms sowie Abwesenheit von Gefäßinvasion und Lymphknotenmetastasen. Vorhandensein von pTis ist anzugeben.	2b	D	+
▪ IHC zum Nachweis minimalen Residualtumors (LK)	2b	B	+/-
▪ Angabe von ypTN-Status nach neoadj. Therapie	5	D	++
▪ Erneute Bestimmung der Hormonrezeptoren und des HER2-Status am Residualtumor	5	D	+/-
▪ Intraoperativer Schnellschnitt (verminderte Sensitivität)	5	D	-
▪ Tumorregression-Scores: RCB-Score oder 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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received neoadjuvant chemotherapy. *Histopathology*. 2007;50(4):409-417. doi:10.1111/j.1365-2559.2006.02419.x.

#### 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, Seinige UL, Lieber CP, Baloch Z. 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.

## Zusatzuntersuchungen: Bestimmung des ER mittels IHC

	Oxford		
	LoE	GR	AGO
■ Immunhistochemischer Nachweis am Paraffinschnitt	1a	A	++
■ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 1\%$ ; niedrig positiv bei $\geq 1\%$ bis $10\%$ )	1a	A	++
■ Färbeintensität	4	D	+
■ Ausschließlich Allred Score (0–8), Remmele Score (0–12)	4	D	-
■ Reevaluation am Exzidat, wenn unklarer Befund an der Stanze oder triple-negativer Tumor	5	D	+

### ASCO/CAP Guideline for ER- and PR-testing

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### IHC-testing for ER-positivity

1. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). *Eur J Cancer*. 2017;75:284-298. doi:10.1016/j.ejca.2017.01.017.
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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.

 <p>© AGO e. V. in der DGOG e.V. sowie in der DKG e.V.</p> <p>Guidelines Breast Version 2023.1D</p> <p>www.ago-online.de</p> <p>FORSCHEN LEBEN HEILEN</p>	Reference	Patients	Results
	Sanford, R. A. <i>et al.</i> <i>Cancer</i> <b>121</b> , 3422–3427 (2015). DOI: 10.1002/cncr.29572	314 Pat. 1–9% ER, Anteil BRCA mutierter Fälle wie bei ER -	High Incidence of Germline BRCA Mutation in Patients with ER Low-Positive/PR Low-Positive/HER-2 neu Negative Tumors
	Deyarmin, B. <i>et al.</i> <i>Ann Surg Oncol</i> <b>20</b> , 87–93 (2013). DOI: 10.1245/s10434-012-2588-8	26 Pat. 1–10% ER, Genexpression eher wie TN oder HER2 enr	Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype
	Prabhu, J. S. <i>et al.</i> <i>J Cancer</i> <b>5</b> , 156–165 (2014) DOI: 10.7150/jca.7668	21 Pat. 1–10% ER, Genexpression wie ER-, Überleben < ER+	A Majority of Low (1–10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors
	Yi, M. <i>et al.</i> <i>Annals of Oncology</i> <b>25</b> , 1004–1011 (2014). DOI: 10.1093/annonc/mdu053	251 Pat. 1–9% ER Überleben = ER-	Which threshold for ER positivity? a retrospective study based on 9639 patients

### 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).
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5. Chen, T. *et al.* Borderline ER-Positive Primary Breast Cancer Gains No Significant Survival Benefit From Endocrine Therapy: A Systematic Review and Meta-Analysis. *Clinical breast cancer* **18**, 1–8 (2018).
6. 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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11. Sanford, R. A. *et al.* High incidence of germline BRCA mutation in patients with ER low-positive/PR low-positive/HER-2 neu negative tumors. *Cancer* **121**, 3422–3427 (2015).
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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).
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## Zusatzuntersuchungen: Bestimmung des PR mittels IHC

	Oxford		
	LoE	GR	AGO
■ Immunhistochemischer Nachweis am Paraffinschnitt	1a	A	++
■ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 10\%$ )	1a	A	++
■ Ausschließlich Allred Score (0–8), Remmele Score (0–12)	4	D	-

### 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
2. 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

### Prognostic significance

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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.

## Zusätzliche Untersuchungen: Molekulare Bestimmung von ER/PR

- Bestimmung der Hormonrezeptoren auf Einzelgenebene durch validierte Genexpressions-Testkits
- Ausschließliche Bestimmung der Expression der Hormonrezeptoren durch RNA-Quantifizierung
- Verwendung der molekularen Rezeptorbestimmung zur Subtypisierung

Oxford		
LoE	GR	AGO
3b	A	+/-
5	D	-
3b	A	+/-

### 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.
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## HER2-Bestimmung mittels IHC

	Oxford		
	LoE	GR	AGO
▪ <b>3+ Färbemuster:</b> HER2 + wenn starke komplette zirkuläre Membranfärbung von > 10% invasiver Zellen	1a	A	++
▪ <b>2+ Färbemuster:</b> Wenn > 10% zirkuläre, schwache/mäßige Membranfärbung oder ≤ 10% stark, U-förmig bei mikropapillären Ca.: ISH erforderlich (CISH, SISH, FISH)	1a	A	++
▪ <b>1+ Färbemuster:</b> bei >10% unvollständiger Membranfärbung, die schwach oder kaum wahrnehmbar ist	1a	A	+
▪ <b>0 Färbemuster:</b> Nachbestimmung bei Möglichkeit der Applikation von Trastuzumab-Deruxatecan*	5	D	++
▪ <b>HER2-low:</b> 1+ oder 2+ /ISH negativ	1b	A	++

\* Wegen Heterogenität und Therapierelevanz

### 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.

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## HER2-Bestimmung: ISH bei IHC 2+

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ Einfärben In-Situ-Hybridisierung (ISH):                             <ul style="list-style-type: none"> <li>■ HER2 + wenn <math>\geq 6</math> Signale in mindestens 20 kohäsiven Zellen</li> <li>■ negativ bei <math>&lt; 4</math> Signalen/Kern</li> <li>■ 2-Farben ISH empfohlen bei <math>\geq 4</math> und <math>&lt; 6</math> Signalen / Kern</li> </ul> </li> <li>■ Zweifarben In-Situ-Hybridisierung (ISH):                             <ul style="list-style-type: none"> <li>■ Gruppe 1: Ratio <math>\geq 2.0</math> und HER2-Signals/Kern <math>\geq 4.0</math> -&gt; HER2+</li> <li>■ Gruppe 2: Ratio <math>\geq 2.0</math> und HER2-Signals/Kern <math>&lt; 4.0</math> -&gt; HER2- (kein Nutzen einer anti-HER2 Therapie)</li> <li>■ Gruppe 3: Ratio <math>&lt; 2.0</math> und HER2-Signals/Kern <math>\geq 6.0</math> -&gt; HER2+ (Nutzen einer anti-HER2 Therapie jedoch unklar)</li> <li>■ Gruppe 4: Ratio <math>&lt; 2.0</math> und HER2-Signals/Kern <math>\geq 4.0</math> und <math>&lt; 6</math> -&gt; HER2- (kein Nutzen einer anti-HER2 Therapie)</li> <li>■ Gruppe 5: Ratio <math>&lt; 2.0</math> und HER2-Signals/Kern <math>&lt; 4.0</math> -&gt; HER2-</li> </ul> </li> </ul>	3a	C	++
	3a	D	++

### ASCO/CAP Guideline on HER2-Testing

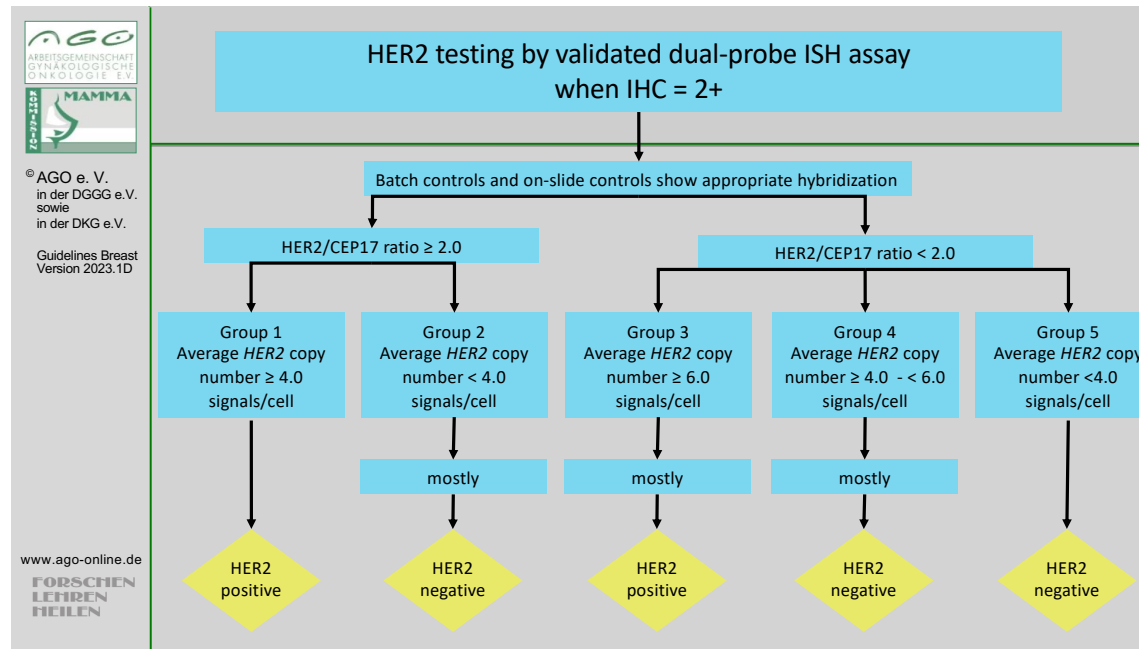
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### ISH HER2-Testing

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HEILEN

## 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

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## Zusätzliche Untersuchungen: Molekulare Bestimmung von HER2

- Therapieentscheidungen sollten nur auf IHC und ISH basieren
- Bestimmung des HER2-Status durch validierte Genexpressions-Testkits
- Bestimmung der HER2-Amplifikation durch NGS
- Verwendung der molekularen HER2-Bestimmung zur Subtypisierung

Oxford		
LoE	GR	AGO
1a	A	++
3b	B	-
5	D	-
3b	B	+/-

### Genomic and gene expression analysis of HER2

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## Zusatzuntersuchungen: Ki-67 Bestimmung

	Oxford		
	LoE	GR	AGO
▪ <b>Auszählung von Zellkernen an der Invasionsfront des Tumors</b>	5	D	++
▪ <b>Semiquantitative Schätzung oder Auszählen an Stanzbiopsaten</b>	2	A	++
▪ <b>Berücksichtigung auch schwach positiver Zellkerne</b>	5	D	++
▪ <b>Angabe des Ki-67 positiver Tumorzellen in Prozent</b>	5	D	++
▪ <b>Etablierung laborinterner Standards und Schwellenwerte</b>	5	D	++
▪ <b>Bildanalyse zur Objektivierung der Ki-67 Auszählung</b>	5	D	+
▪ <b>Neu-Bestimmung Ki-67 nach Kurzzeit präoperativer (2-4 Wochen) endokriner Induktion (ypTNM trotz Kurzzeit)*</b>	1b	B	+

\* Siehe Kapitel neoadjuvante Therapie

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#### Ki67 als dynamischer Marker nach Kurzzeit endokriner Therapie

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## Prädiktive PD-L1 Bestimmung

### Immunhistochemischer Nachweis

**Immun-Score (IC):** Zytoplasmatische Positivität von mindestens 1% des leukozytären Begleitinfiltrates (Lymphozyten, Makrophagen, Plasma- zellen, Granulozyten außerhalb von Abszessen) zur Prädiktion einer **Atezolizumab** Wirksamkeit beim triple negativen metastasierten Mammakarzinom

Primärtumor- oder Metastasengewebe verwendbar

Einsatz von Primärantikörpern äquivalent zur Impassion 130 Studie

**Combined positive score (CPS):** Zahl positiv markierter Zellen (Tumor, Lymphozyten und Makrophagen) dividiert durch die Tumorzellzahl mal 100 ( $\geq 10$  = positiv) zur Prädiktion einer **Pembrolizumab** Wirksamkeit beim triple negativen Mammakarzinom (durch FDA zugelassen, EMA ausstehend)

### Oxford

#### LoE GR AGO

2 A ++

2 A ++

3 B +

3 B +/-

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## Mutationsdiagnostik beim mBC: „Precision medicine“ für zielgerichtete Therapien

Alteriertes Gen	Therapierelevanz	Genregion	Ausgangsmaterial	Oxford		
				LOE	GR	AGO
BRCA1, BRCA2	PARP Inhibitor	Alle Exone	Keimbahn: Blutzellen Somatisch: Gewebe	1b 2b	A B	++ +/-
PIK3CA	Alpelisib	Exone 7,9 und 20	Primärtumor, Metastasen, Plasma	1b	A	++
HER2-Mutation (unabh. vom HER2-Status)	Neratinib, Lapatinib	Kinase- und extrazelluläre Domänen; S310, L755, V777, Y772_A775dup	Primärtumor, Metastasen, Plasma	4	C	+/-
ESR1	Resistenz gegenüber AI	Exone 4,7 und 8	Metastasen, Plasma	2b	B	+/-
NTRK Genfusion	Larotrectinib, Entrectinib	Fusions- und Spleißvarianten	Tumorgewebe, ins. Sekretorisches Mammakarzinom	2a	B	+
MSI	Pembrolizumab	Mikrosatelliten- Instabilität	Gewebe	2a	B	+

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## MSI

FDA Zulassung entitätsübergreifend (23.5.17): Full prescribing information for pembrolizumab is available at:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/125514s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf)

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