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Guidelines Breast
Version 2021.1D

Pathologie

Screened data bases: PubMed 2020.

Search Query:

(Breast Diseases/PA[mh] AND ("2010/01/01"[dp] : "2020/01/01"[dp]) AND ("english"[la] OR "german"[la])

Guidelines screened

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.National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. January 2020:1-223.

3.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.

4.Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International

Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol*. 2019;30(10):1541-1557. doi:10.1093/annonc/mdz235.

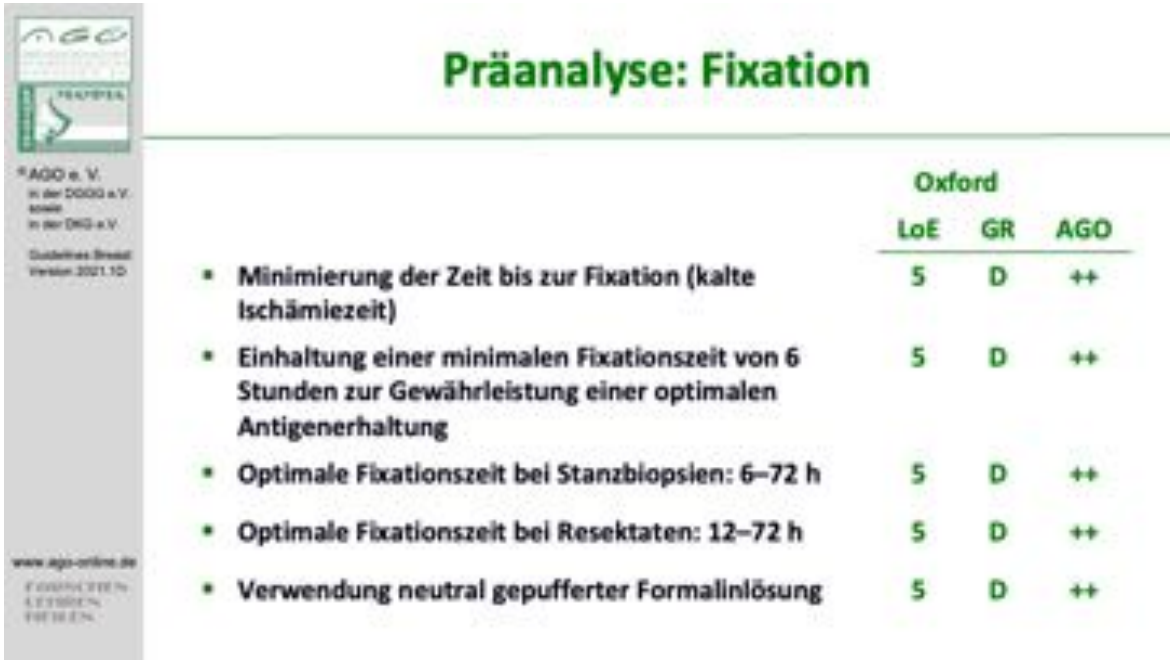
5. Untch M, Thomssen C, Bauerfeind I, et al. Primary Therapy of Early Breast Cancer: Evidence, Controversies, Consensus: Spectrum of Opinion of German Specialists on the 16th St. Gallen International Breast Cancer Conference (Vienna 2019). *Geburtsh Frauenheilkd*. 2019;79(6):591-604. doi:10.1055/a-0897-6457.

6.Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). *S3-Leitlinie Früherkennung, Diagnostik, Therapie Und Nachsorge Des Mammakarzinoms*. 2017:1-448.

7.Wells CA. Pathology_Update_Breast_Screening. 2014:1-48. http://www.euref.org/european-guidelines.

8.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.

9.Schweizerische Gesellschaft für Pathologie (2002). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. https://sgpath.ch/docs/QRL/QRL_SGPath_Mamma_2017.pdf



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.

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., 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
6. Bruzzone, 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

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

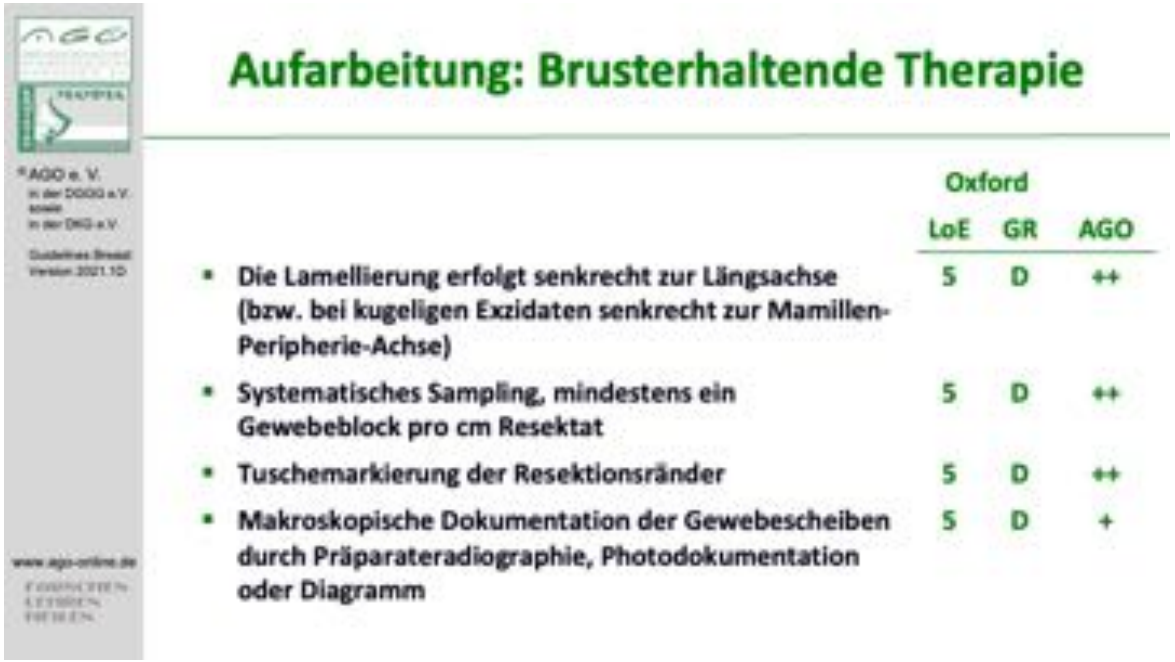
Statement: Routine evaluation of ER/PgR and HER-2 status

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



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.

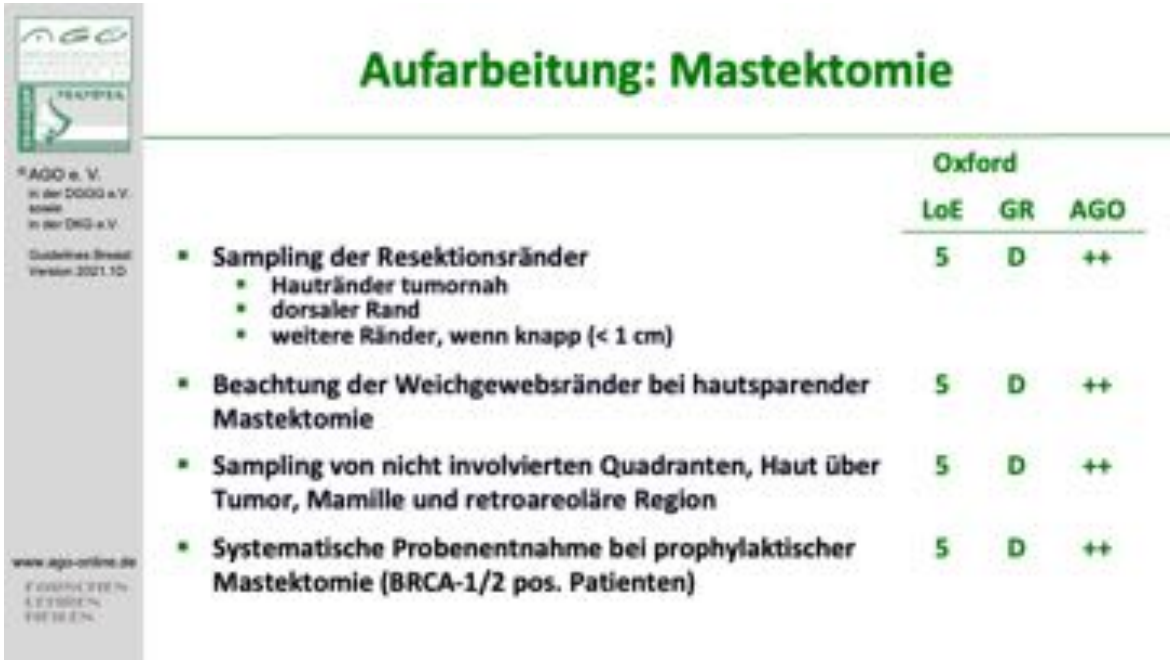
Systematic Sampling

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.



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.

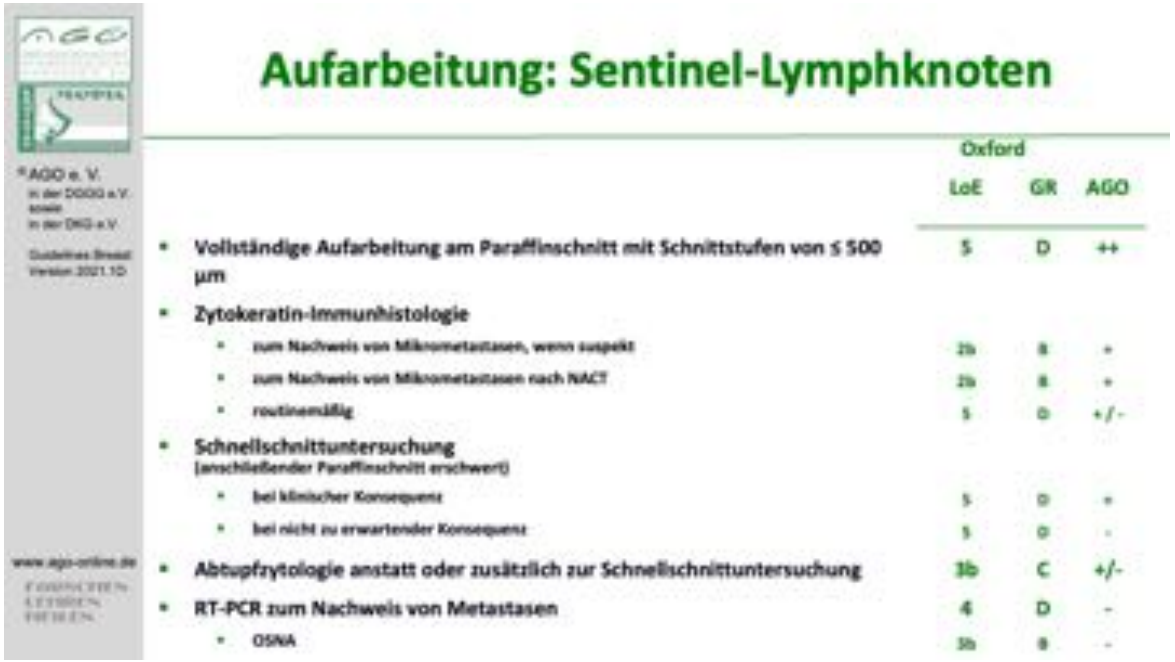
13. Ho CM, Mak CKL, Lau Y, Cheung WY, Chan MCM, Hung WK. Skin involvement in invasive breast carcinoma: safety of skin-sparing mastectomy. *Ann Surg Oncol*. 2003;10(2):102-107. doi:10.1245/aso.2003.05.001.

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.



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 ≥ 500 µm 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: 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, Torrenga 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 (Reinthaler 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

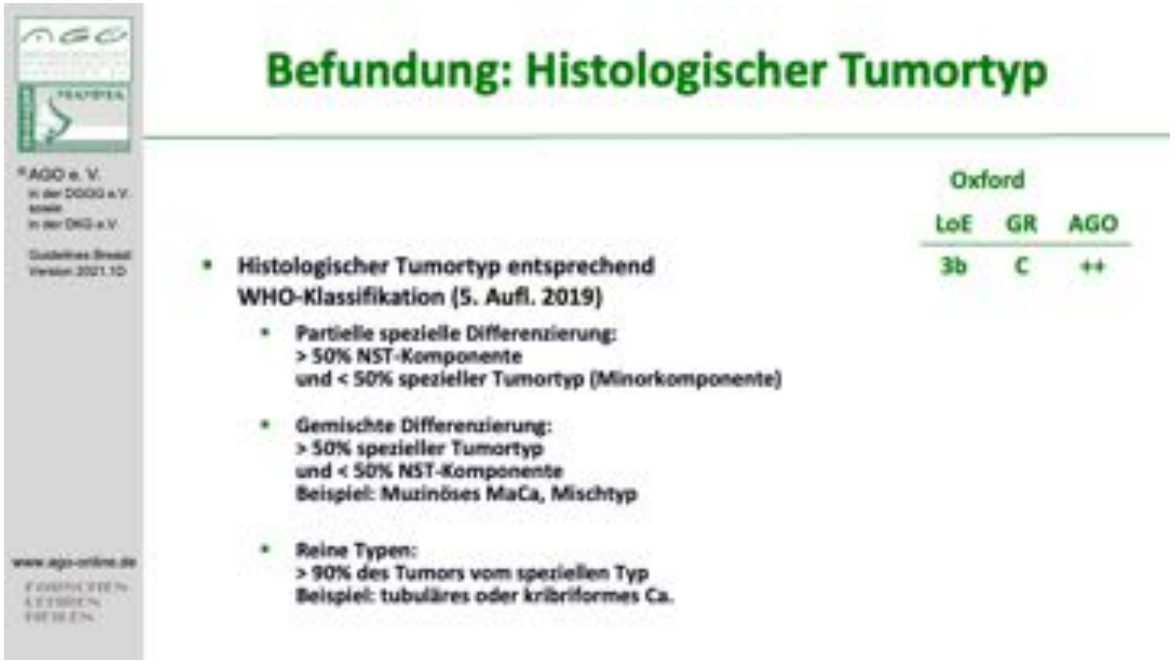
1.Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthaler R, Helfer L, Hrsg.). http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/

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

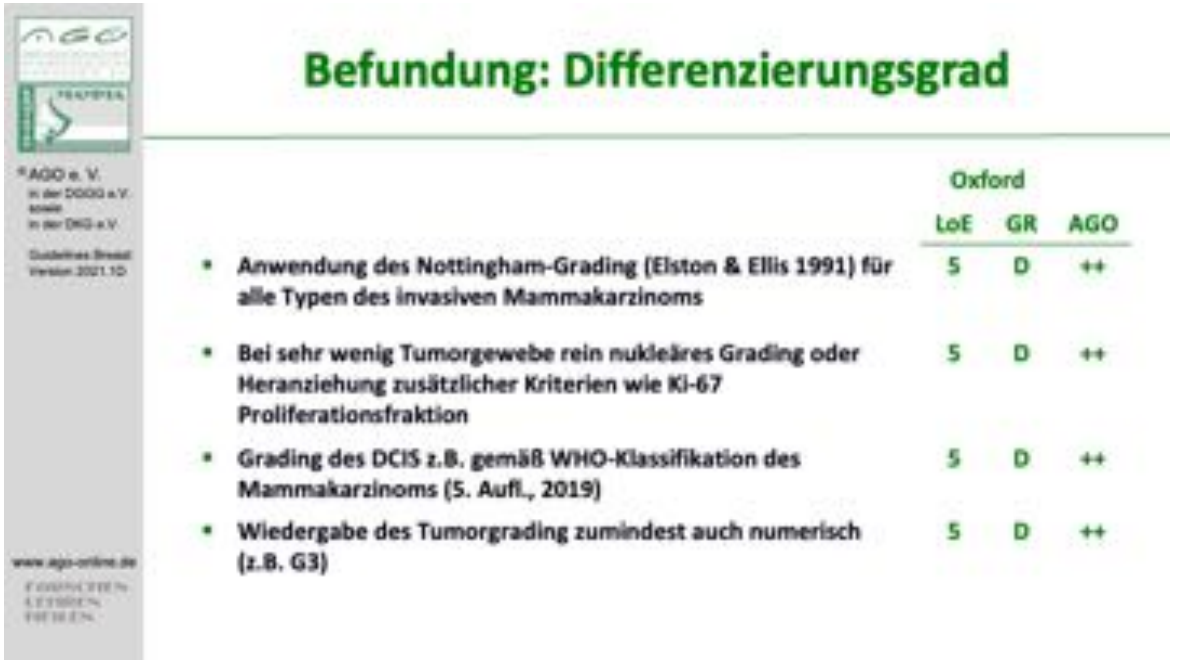
Statement: Non-palpable lesions or lesions < 1 cm

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.



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



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.

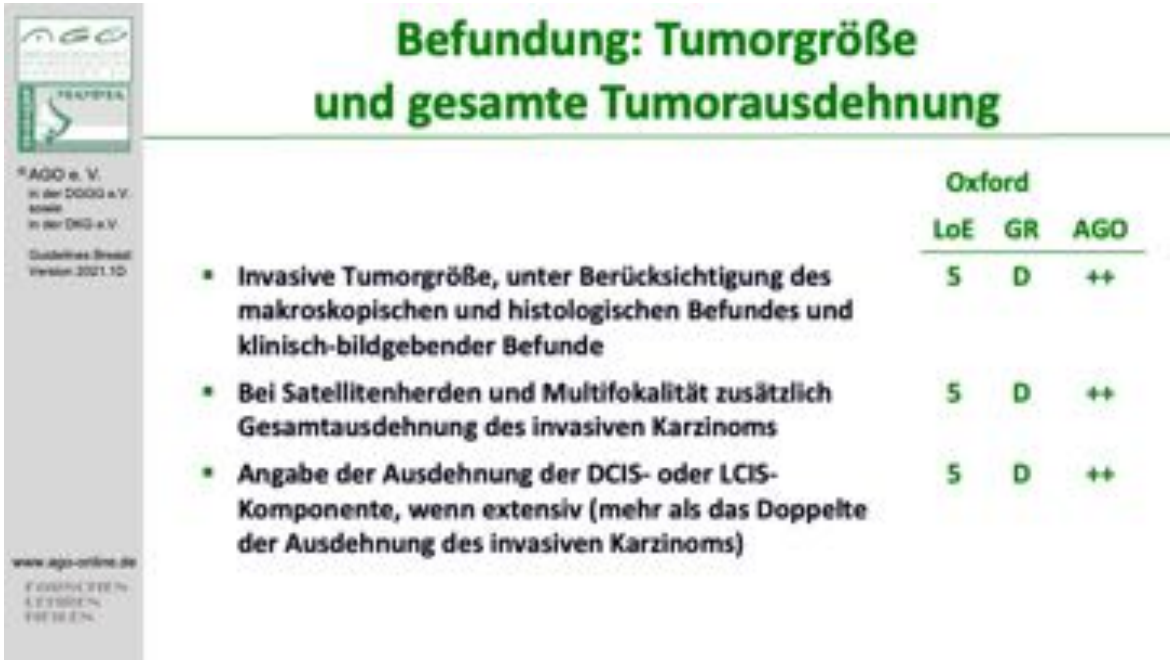
7. Rakha EA, El-Sayed ME, Lee AHS, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. *J Clin Oncol*. 2008;26(19):3153-3158. doi:10.1200/JCO.2007.15.5986.

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.



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.

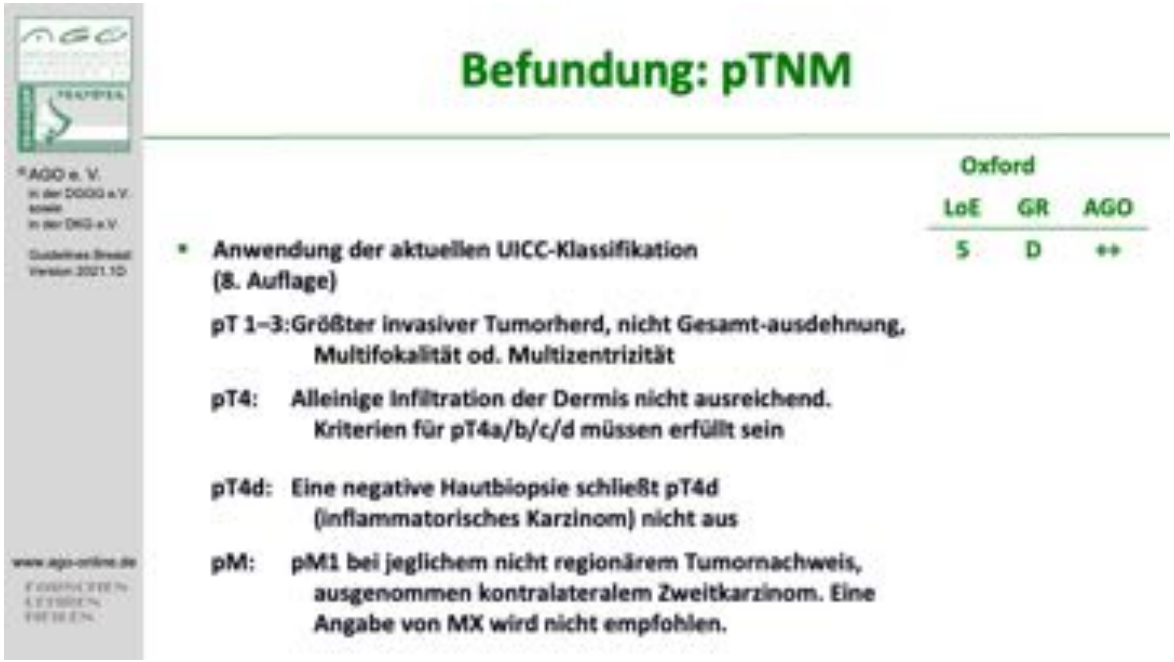
Extensive intraductal component (EIC)

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



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: Involvemant of the skin

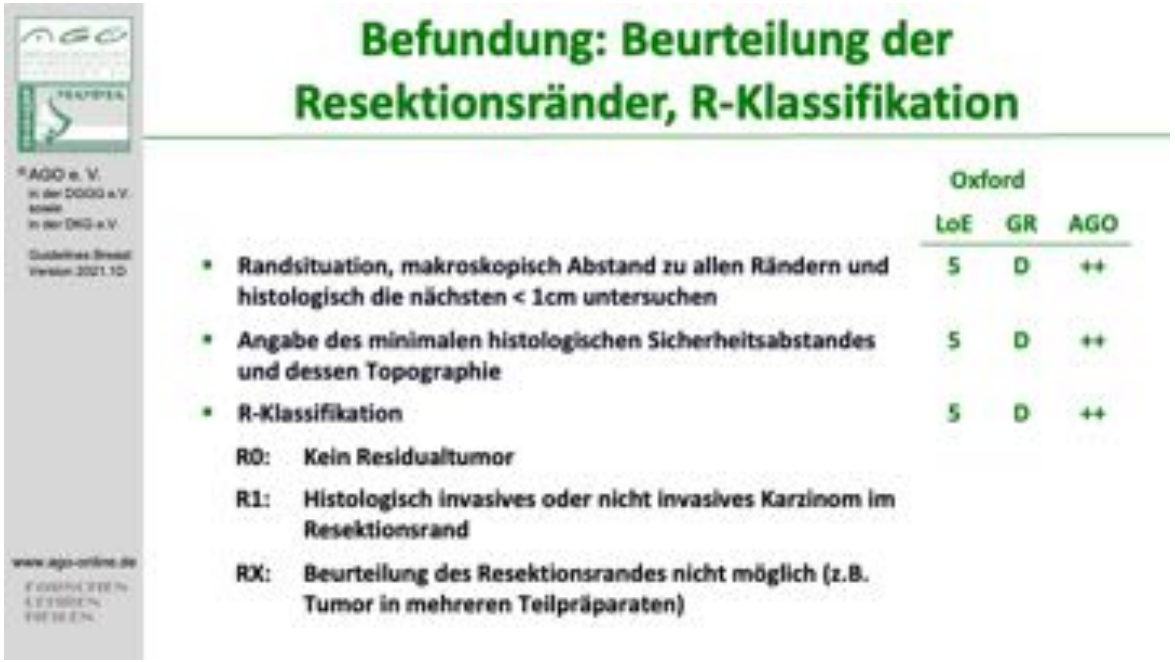
1. Wieland, A., Louwman, M., Voogd, A., et al. (2004). Determinants of prognosis in breast cancer patients with tumor involvement of the skin (pT4b). The Breast Journal, 10(2), 123–128. doi:21279 [pii]

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



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

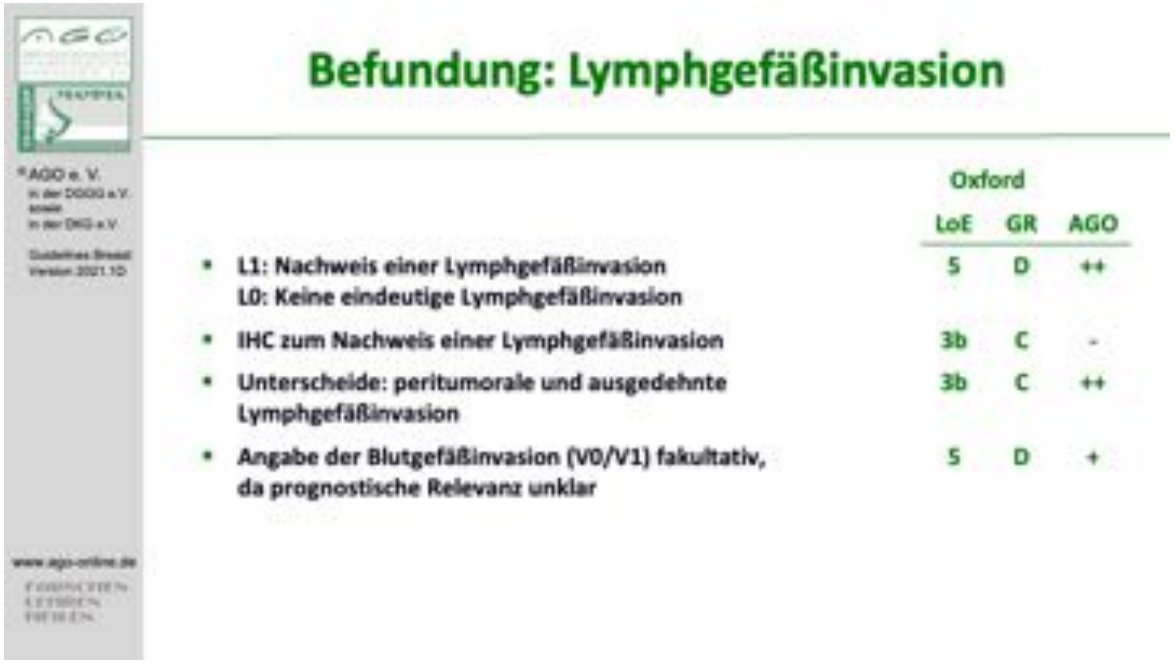
6.Keskek, M., Kothari, M., Ardehali, B. et al. (2004). Factors predisposing to cavity margin positivity following conservation surgery for

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.



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. Jet 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.

Definition and impact of predominant lymphocytic infiltration

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.

2.Dieci MV, Radosevic-Robin N, Fineberg S, et al. Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: A report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer. *Semin Cancer Biol*. 2018;52(Pt 2):16-25. doi:10.1016/j.semcancer.2017.10.003.

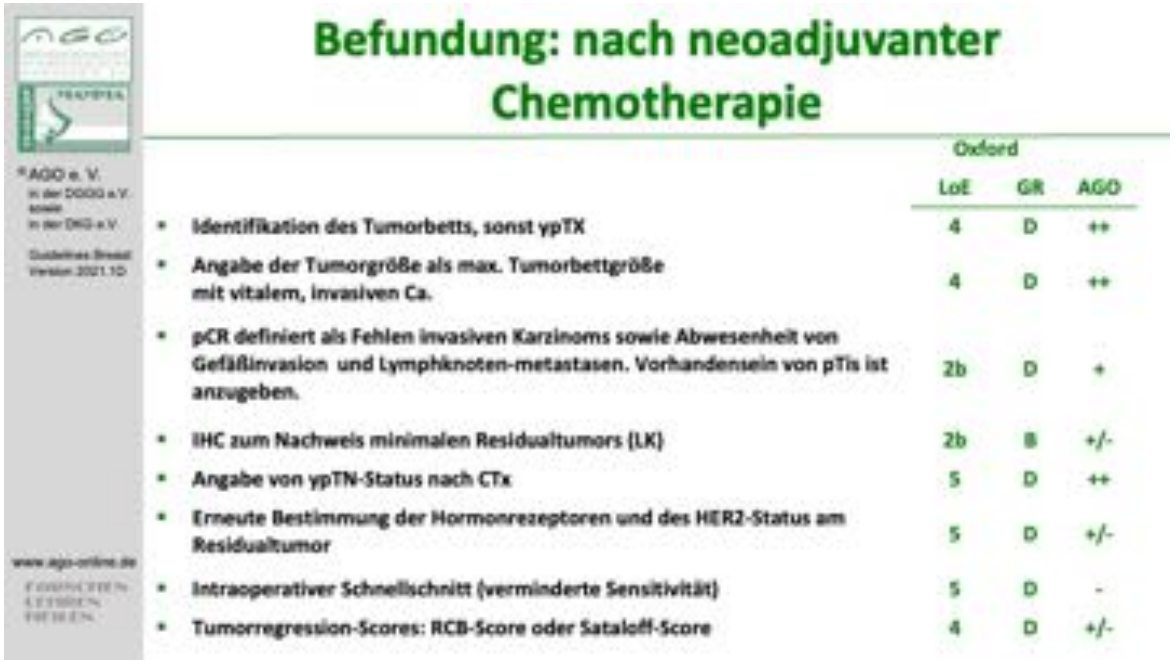
3.Grigoriadis A, Gazinska P, Pai T, et al. Histological scoring of immune and stromal features in breast and axillary lymph nodes is prognostic for distant metastasis in lymph node-positive breast cancers. *J Pathol Clin Res*. 2018;4(1):39-54. doi:10.1002/cjp2.87.

4.Tramm T, Di Caterino Tina, Jylling A-MB, et al. Standardized assessment of tumor-infiltrating lymphocytes in breast cancer: an evaluation of inter-observer agreement between pathologists. *Acta Oncol*. 2018;57(1):90-94. doi:10.1080/0284186X.2017.1403040.

5.Denkert C, Minckwitz von G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018;19(1):40-50. doi:10.1016/S1470-2045(17)30904-X.

6. Salgado R, Denkert C, Demaria S, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol*. 2015;26(2):259-271. doi:10.1093/annonc/mdu450.

7.Denkert C, Salgado R, Demaria S. Standardized evaluation of Tumor-Infiltating Lymphocytes (TIL) in Breast Cancer for daily clinical and research practice or clinical trial setting. In:; 2014:1-14.



Befundung: nach neoadjuvanter Chemotherapie

	Oxford		
	LoE	GR	AGO
• Identifikation des Tumorbetts, sonst ypTX	4	D	++
• Angabe der Tumorgröße als max. Tumorbettgröße mit vitalem, invasiven Ca.	4	D	++
• pCR definiert als Fehlen invasiven Karzinoms sowie Abwesenheit von Gefäßinvasion und Lymphknoten-metastasen. Vorhandensein von pTis ist anzugeben.	2b	D	+
• IHC zum Nachweis minimalen Residualtumors (LK)	2b	B	+/-
• Angabe von ypTN-Status nach CTx	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

2.Bossuyt V, Provenzano E, Symmans WF, et al. Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration. *Ann Oncol*. 2015;26(7):1280-1291. doi:10.1093/annonc/mdv161

3.Sahoo S, Lester SC. Pathology of breast carcinomas after neoadjuvant chemotherapy: an overview with recommendations on specimen processing and reporting. *Arch Pathol Lab Med*. 2009;133(4):633-642. doi:10.1043/1543-2165-133.4.633

4.Fan F. Evaluation and reporting of breast cancer after neoadjuvant chemotherapy. *Open Pathology Journal*. 2009;3:58-63

5.Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *J Clin Oncol*. 2008;26(5):814-819. doi:10.1200/JCO.2007.15.3510

6.Pinder SE, Provenzano E, Earl H, Ellis IO. Laboratory handling and histology reporting of breast specimens from patients who have

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

3.Naidoo K, Parham DM, Pinder SE. An Audit of Residual Cancer Burden Reproducibility in a UK context. *Histopathology*. August 2016. doi:10.1111/his.13054

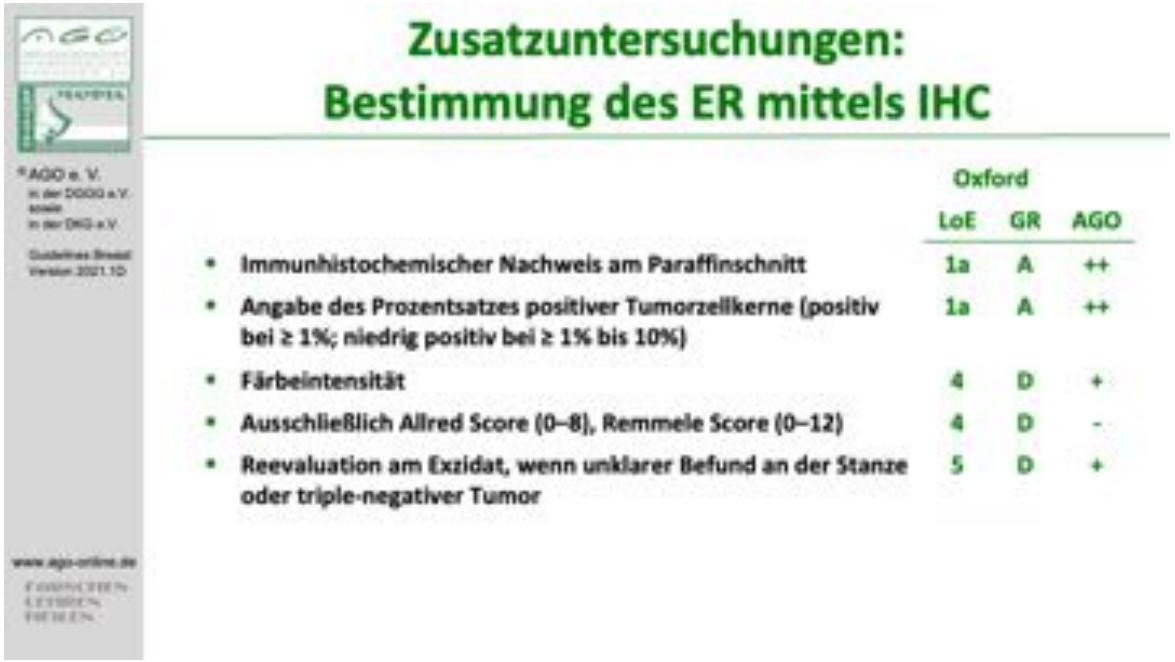
4.Peintinger F, Sinn B, Hatzis C, et al. Reproducibility of residual cancer burden for prognostic assessment of breast cancer after neoadjuvant chemotherapy. *Mod Pathol*. 2015;28(7):913-920. doi:10.1038/modpathol.2015.53

5.Sheri A, Smith IE, Johnston SR, et al. Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. *Ann Oncol*. 2015;26(1):75-80. doi:10.1093/annonc/mdu508

6.Symmans, W. F., Peintinger, F., Hatzis, C., et al. (2007). Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 25(28), 4414–4422.

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.



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

2.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.

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.

2.Schrijver WAME, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis. *J Natl Cancer Inst*. 2018;110(6):568-580. doi:10.1093/jnci/djx273.

3.Traub L, Thill M, Nitschmann S. 20-Jahres-Ergebnisse einer 5-jährigen Hormontherapie bei Mammakarzinom : Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Internist (Berl)*. 2018;59(4):410-412. doi:10.1007/s00108-018-0398-1.

4. 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

5.Allred, D. C., Carlson, R. W., Berry, D. A., et al. (2009). NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing 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

6.Gown, A. M. (2008). Current issues in ER and HER2 testing by IHC in breast cancer. Modern Pathology, 21, S8–S15

7.Hammond, M. E., Hayes, D. F., & Wolff, A. C. (2011). Clinical Notice for American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations on ER/PgR and HER2 Testing in Breast Cancer. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(15), e458–e458.

8.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. Epub 2006 Nov 20.

9.Hammond et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med (2010) vol. 134 (6) pp. 907-22

10.Rocha R, Nunes C, Rocha G et al. Rabbit monoclonal antibodies show higher sensitivity than mouse monoclonals for estrogen and progesterone receptor evaluation in breast cancer by immunohistochemistry. Pathol Res Pract. 2008;204(9):655-62. Epub 2008 Jun 18.

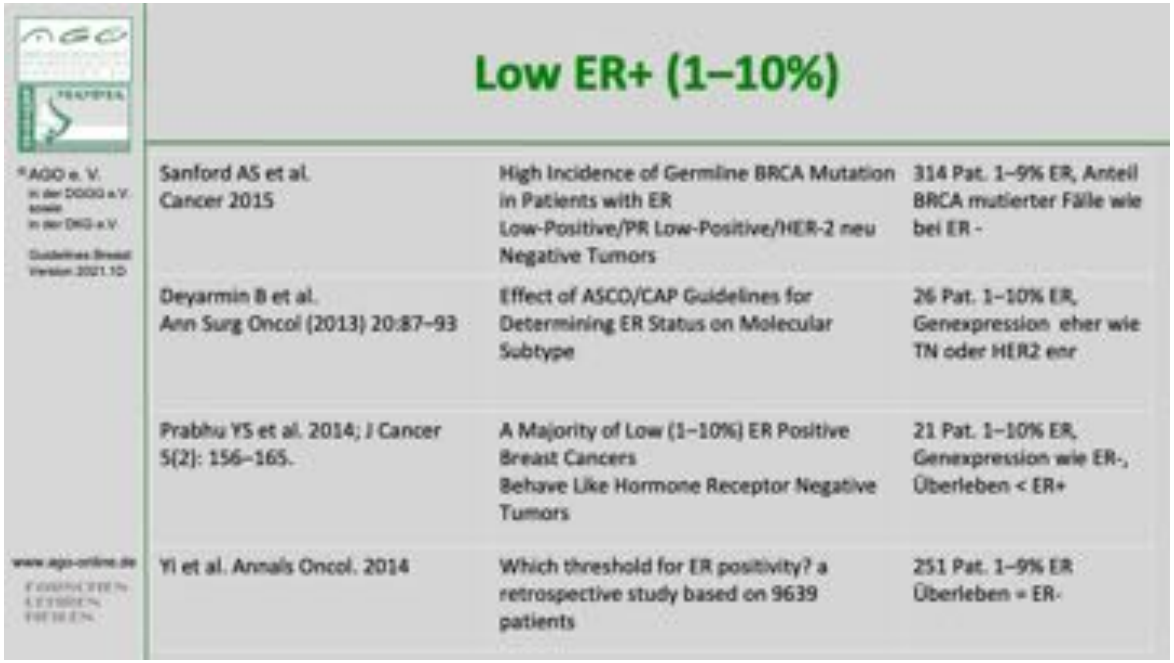
IHC Scores

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) fur den immunhistochemischen Ostrogenrezeptor-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.



Low ER+ (1–10%)

Sanford AS et al. Cancer 2015	High Incidence of Germline BRCA Mutation in Patients with ER Low-Positive/PR Low-Positive/HER-2 neu Negative Tumors	314 Pat. 1–9% ER, Anteil BRCA mutierter Fälle wie bei ER -
Deyarmin B et al. Ann Surg Oncol (2013) 20:87–93	Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype	26 Pat. 1–10% ER, Genexpression eher wie TN oder HER2 enr
Prabhu YS et al. 2014; J Cancer 5(2): 156–165.	A Majority of Low (1–10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors	21 Pat. 1–10% ER, Genexpression wie ER-, Überleben < ER+
Yi et al. Annals Oncol. 2014	Which threshold for ER positivity? a retrospective study based on 9639 patients	251 Pat. 1–9% ER Überleben = ER-

Low ER+ Group

1.Poon IK, Tsang JY, Li J, Chan S-K, Shea K-H, Tse GM. The significance of highlighting the oestrogen receptor low category in breast cancer. *Br J Cancer*. 2020;123(8):1223-1227. doi:10.1038/s41416-020-1009-1.

2.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.

3.Landmann A, Farrugia DJ, Zhu L, et al. Low Estrogen Receptor (ER)-Positive Breast Cancer and Neoadjuvant Systemic Chemotherapy: Is Response Similar to Typical ER-Positive or ER-Negative Disease? *Am J Clin Pathol*. 2018;150(1):34-42. doi:10.1093/ajcp/aqy028.

4.Chen T, Zhang N, Moran MS, Su P, Haffty BG, Yang Q. Borderline ER-Positive Primary Breast Cancer Gains No Significant Survival Benefit From Endocrine Therapy: A Systematic Review and Meta-Analysis. *Clinical breast cancer*. 2018;18(1):1-8. doi:10.1016/j.clbc.2017.06.005.

5.Reddy SM, Barcenas CH, Sinha AK, 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. *Br J Cancer*. 2018;118(1):17-23. doi:10.1038/bjc.2017.379.

6.Fujii T, Kogawa T, Dong W, et al. Revisiting the definition of estrogen receptor positivity in HER2-negative primary breast cancer. *Ann*

Oncol. 2017;28(10):2420-2428. doi:10.1093/annonc/mdx397.

7. Viale G. Controversies in treatment selection for patients with equivocal ER and HER2 results. *Breast*. 2017;34 Suppl 1:S61-S63. doi:10.1016/j.breast.2017.06.030.

8.Nordenskjöld A, Fohlin H, Fornander T, Löfdahl B, Skoog L, Stål O. Progesterone receptor positivity is a predictor of long-term benefit from adjuvant tamoxifen treatment of estrogen receptor positive breast cancer. *Breast Cancer Res Treat*. 2016;160(2):313-322. doi:10.1007/s10549-016-4007-5.

9.Sanford RA, Song J, Gutierrez-Barrera AM, et al. High incidence of germline BRCA mutation in patients with ER low-positive/PR low-positive/HER-2 neu negative tumors. *Cancer*. 2015;121(19):3422-3427. doi:10.1002/cncr.29572.

10.Balduzzi A, Bagnardi V, Rotmensz N, et al. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. *Clinical breast cancer*. 2014;14(4):258-264. doi:10.1016/j.clbc.2013.10.019

11.Yi M, Huo L, Koenig KB, et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. *Ann Oncol*. 2014;25(5):1004-1011. doi:10.1093/annonc/mdu053

12. Gloyeske NC, Dabbs DJ, Bhargava R. Low ER+ breast cancer: Is this a distinct group? *Am J Clin Pathol*. 2014;141(5):697-701. doi:10.1309/AJCP34CYSATWFDPQ

13. Prabhu JS, Korlimarla A, Desai K, et al. A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors. *J Cancer*. 2014;5(2):156-165. doi:10.7150/jca.7668

14. Reisenbichler ES, Lester SC, Richardson AL, Dillon DA, Ly A, Brock JE. 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. *Am J Clin Pathol*. 2013;140(4):487-494. doi:10.1309/AJCP1RF9FUIZRDPI

15. Deyarmin B, Kane JL, Valente AL, et al. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. *Ann Surg Oncol*. 2013;20(1):87-93. doi:10.1245/s10434-012-2588-8

16. Rakha EA, Lee AHS, Roberts J, et al. Low-estrogen receptor-positive breast cancer: the impact of tissue sampling, choice of antibody, and molecular subtyping. *J Clin Oncol*. 2012;30(23):2929–30–authorreply2931. doi:10.1200/JCO.2012.43.2831.

17. Iwamoto T, Booser D, Valero V, et al. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. *J Clin Oncol*. 2012;30(7):729-734. doi:10.1200/JCO.2011.36.2574.

18.Kim C, Tang G, Pogue-Geile KL, et al. Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. *J Clin Oncol*. 2011;29(31):4160-4167. doi:10.1200/JCO.2010.32.9615

19.Early Breast Cancer Trialists Collaborative Group EBCTCG, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378(9793):771-784. doi:10.1016/S0140-6736(11)60993-8.

20.Rhodes A, Maurice YM, Sheard JD, Jasani B, Helliwell TR. The oestrogen receptor-negative/progesterone receptor-positive breast tumour: a biological entity or a technical artefact? *SciMed Central*. 2009;62(1):95-96. doi:10.1136/jcp.2008.060723.

21.Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. *J Clin Oncol*. 2008;26(7):1059-1065. doi:10.1200/JCO.2007.12.9437.

22.Viale G, Regan MM, Maiorano E, 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. *J Clin Oncol*. 2007;25(25):3846-3852. doi:10.1200/JCO.2007.11.9453.

23.Yamashita H, Yando Y, Nishio M, et al. Immunohistochemical evaluation of hormone receptor status for predicting response to endocrine therapy in metastatic breast cancer. *Breast cancer (Tokyo, Japan)*. 2006;13(1):74-83. doi:10.2325/jbcs.13.74.

24.Mann GB, Fahey VD, Feleppa F, Buchanan MR. Reliance on hormone receptor assays of surgical specimens may compromise outcome in patients with breast cancer. *J Clin Oncol*. 2005;23(22):5148-5154. doi:10.1200/JCO.2005.02.076.

25.Early Breast Cancer Trialists Collaborative Group EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-1717. doi:10.1016/S0140-6736(05)66544-0.

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

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.

2.Prat, A., Cheang, M. C. U., Martin, M., et al. (2013). Prognostic Significance of Progesterone Receptor-Positive Tumor Cells Within Immunohistochemically Defined Luminal A Breast Cancer. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 31(2), 203–209.

Aberrant Expression of ER in triple negative breast cancer

1.Cserni, G., Francz, M., Kálmán, E., et al. (2011). Estrogen receptor negative and progesterone receptor positive breast carcinomas-how frequent are they? Pathology Oncology Research : POR, 17(3), 663–668. doi:10.1007/s12253-011-9366-y

2.Hefti, M. M., Hu, R., Knoblauch, N. W., et al. (2013). Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. Breast Cancer Research : BCR, 15(4), R68.

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) fur den immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

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.

3.Oosterkamp HM, Hijmans EM, Brummelkamp TR, et al. USP9X downregulation renders breast cancer cells resistant to tamoxifen. *Cancer Res*. 2014;74(14):3810-3820. doi:10.1158/0008-5472.CAN-13-1960.

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.

5.Cardoso F, Slaets L, Russo L, et al. 4LBA RNA, protein or gene? ER, PgR and HER2 by local and central pathology review, and microarray readout (by TargetPrint) in the EORTC 10041/BIG 03-04 MINDACT trial. In: Vol 50. Elsevier Ltd and ECCO; 2014:S2. doi:10.1016/S0959-

8049(14)70112-1.

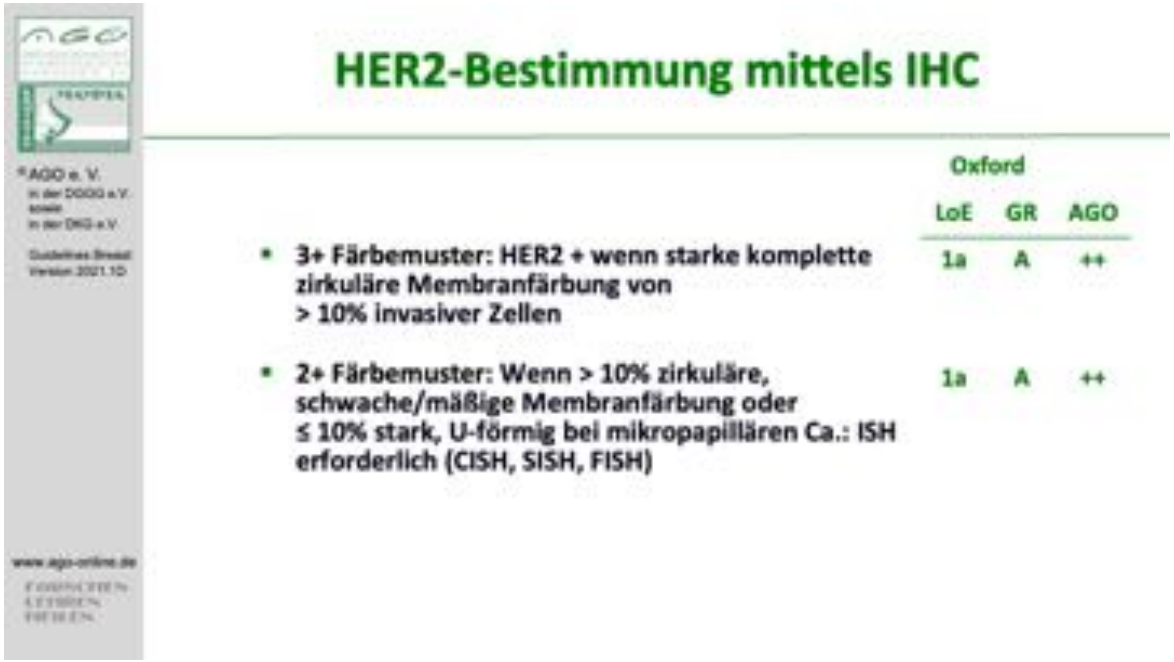
6. Itoh M, Iwamoto T, Matsuoka J, et al. Estrogen receptor (ER) mRNA expression and molecular subtype distribution in ER-negative/progesterone receptor-positive breast cancers. *Breast Cancer Res Treat*. 2014;143(2):403-409. doi:10.1007/s10549-013-2763-z.

7.Pogue-Geile KL, Kim C, Jeong J-H, et al. Predicting degree of benefit from adjuvant trastuzumab in NSABP trial B-31. *J Natl Cancer Inst*. 2013;105(23):1782-1788. doi:10.1093/jnci/djt321.

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.

9.Denkert C, Huober J, Loibl S, et al. HER2 and ESR1 mRNA expression levels and response to neoadjuvant trastuzumab plus chemotherapy in patients with primary breast cancer. *Breast Cancer Res*. 2013;15(1):R11. doi:10.1186/bcr3384.

10.Prat A, Cheang MCU, Martin M, et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. *J Clin Oncol*. 2013;31(2):203-209. doi:10.1200/JCO.2012.43.4134.



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

1.Liu Z-H, Wang K, Lin D-Y, et al. Impact of the updated 2018 ASCO/CAP guidelines on HER2 FISH testing in invasive breast cancer: a retrospective study of HER2 fish results of 2233 cases. *Breast Cancer Res Treat*. 2019;175(1):51-57. doi:10.1007/s10549-019-05148-5.

2.Prat A, Pascual T, De Angelis C, et al. HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. *J Natl Cancer Inst*. April 2019. doi:10.1093/jnci/djz042.

3.Gordian-Arroyo AM, Zynger DL, Tozbikian GH. Impact of the 2018 ASCO/CAP HER2 Guideline Focused Update. *Am J Clin Pathol*. 2019;152(1):17-26. doi:10.1093/ajcp/aqz012.

4.Curado M, Caramelo AS, Eloy C, Polónia A. What to expect from the 2018 ASCO/CAP HER2 guideline in the reflex in situ hybridization

test of immunohistochemically equivocal 2+ cases? *Virchows Arch*. 2019;68(6):394-399. doi:10.1007/s00428-019-02567-z.

5. Schneider F, Jin Y, Van Smaalen K, Gulbahce EH, Factor RE, Li X. The FDA-Approved Breast Cancer HER2 Evaluation Kit (HercepTest; Dako) May Miss Some HER2-Positive Breast Cancers. *Am J Clin Pathol*. 2019;151(5):504-510. doi:10.1093/ajcp/aqy171.

6.Press MF, Seoane JA, Curtis C, et al. Assessment of ERBB2/HER2 Status in HER2-Equivocal Breast Cancers by FISH and 2013/2014 ASCO-CAP Guidelines. *JAMA Oncol*. 2019;5(3):366-375. doi:10.1001/jamaoncol.2018.6012.

7.Rye IH, Trinh A, Saetersdal AB, et al. Intratumor heterogeneity defines treatment-resistant HER2+ breast tumors. *Molecular Oncology*. 2018;12(11):1838-1855. doi:10.1002/1878-0261.12375.

8.Dodson A, Parry S, Ibrahim M, et al. Breast cancer biomarkers in clinical testing: analysis of a UK national external quality assessment scheme for immunocytochemistry and in situ hybridisation database containing results from 199 300 patients. *J Pathol Clin Res*. 2018;4(4):262-273. doi:10.1002/cjp2.112.

9.Pfitzner BM, Lederer B, Lindner J, et al. Clinical relevance and concordance of HER2 status in local and central testing-an analysis of 1581 HER2-positive breast carcinomas over 12 years. *Mod Pathol*. 2018;31(4):607-615. doi:10.1038/modpathol.2017.171.

10.Sorscher S. Reclassifying HER2-equivocal disease. *Breast Cancer Res Treat*. 2018;167(3):823-823. doi:10.1007/s10549-017-4545-5.

11.Tong Y, Chen X, Fei X, et al. Can breast cancer patients with HER2 dual-equivocal tumours be managed as HER2-negative disease? *Eur J Cancer*. 2018;89:9-18. doi:10.1016/j.ejca.2017.10.033.

12.Petrelli F, Tomasello G, Barni S, Lonati V, Passalacqua R, Ghidini M. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res Treat*. 2017;166(2):339-349. doi:10.1007/s10549-017-4419-x.

13.Hou Y, Nitta H, Wei L, et al. HER2 intratumoral heterogeneity is independently associated with incomplete response to anti-HER2 neoadjuvant chemotherapy in HER2-positive breast carcinoma. *Breast Cancer Res Treat*. 2017;166(2):447-457. doi:10.1007/s10549-017-4453-8.

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.

ISH HER2-Testing

1.Hwang HC, Gown AM. Evaluation of Human Epidermal Growth Factor Receptor 2 (HER2) Gene Status in Human Breast Cancer Formalin-Fixed Paraffin-Embedded (FFPE) Tissue Specimens by Fluorescence In Situ Hybridization (FISH). *Methods Mol Biol*. 2016;1406(Chapter 5):61-70. doi:10.1007/978-1-4939-3444-7_5.

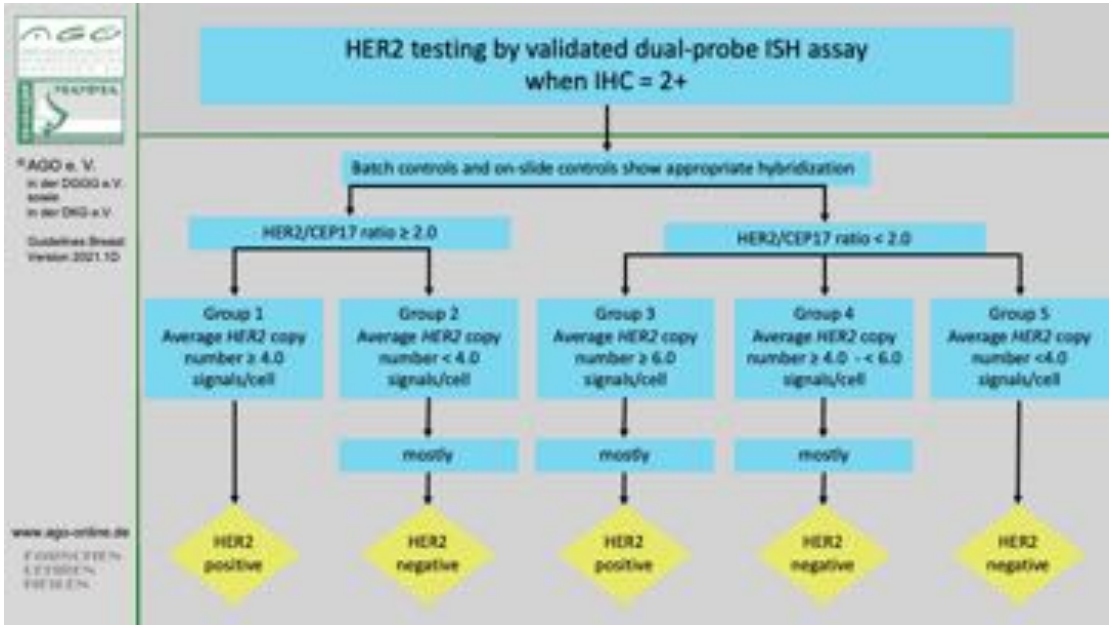
2.Stoss OC, Scheel A, Nagelmeier I, et al. Impact of updated HER2 testing guidelines in breast cancer--re-evaluation of HERA trial fluorescence in situ hybridization data. *Mod Pathol*. 2015;28(12):1528-1534. doi:10.1038/modpathol.2015.112.

3.Starczynski J, Atkey N, Connelly Y, et al. HER2 gene amplification in breast cancer: a rogues' gallery of challenging diagnostic cases: UKNEQAS interpretation guidelines and research recommendations. *Am J Clin Pathol*. 2012;137(4):595-605.

doi:10.1309/AJCPATBZ2JFN1QQC.

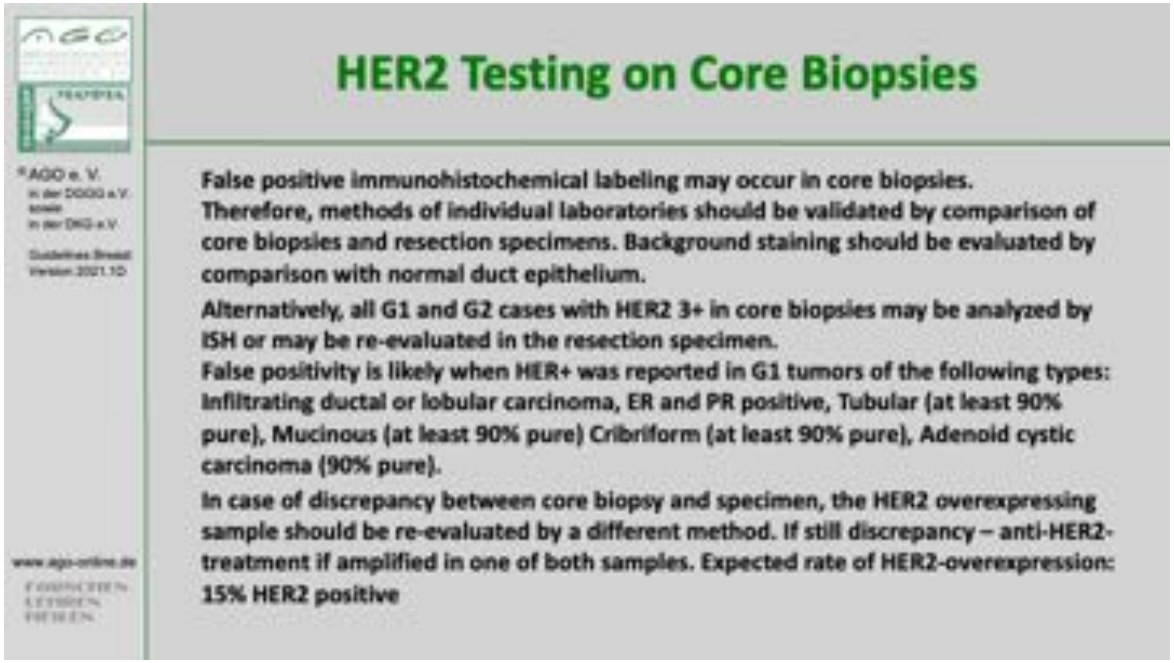
4. Sauter G, Lee J, Bartlett JMS, Slamon DJ, Press MF. Guidelines for Human Epidermal Growth Factor Receptor 2 Testing: Biologic and Methodologic Considerations. *J Clin Oncol*. 2009;27(8):1323-1333. doi:10.1200/JCO.2007.14.8197.

5.Chivukula M, Bhargava R, Brufsky A, Surti U, Dabbs D. Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. *Mod Pathol*. 2008;21(4):363-368. doi:10.1038/modpathol.3801021.



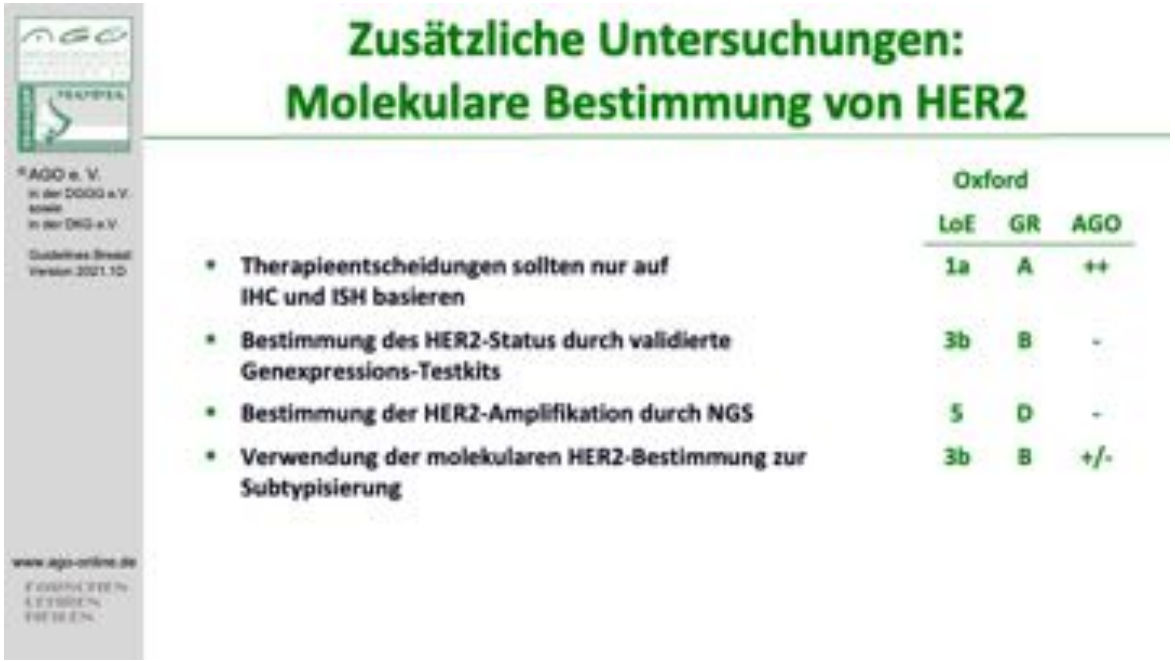
<u>ASCO/CAP Guideline on HER2-Testing</u>

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.



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.



Genomic and gene expression analysis of HER2

1.Prat A, Pascual T, De Angelis C, et al. HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. *J Natl Cancer Inst*. April 2019. doi:10.1093/jnci/djz042.

2.Lesurf R, Griffith OL, Griffith M, et al. Genomic characterization of HER2-positive breast cancer and response to neoadjuvant trastuzumab and chemotherapy-results from the ACOSOG Z1041 (Alliance) trial. *Ann Oncol*. 2017;28(5):1070-1077. doi:10.1093/annonc/mdx048.

3.Ross DS, Zehir A, Cheng DT, et al. Next-Generation Assessment of Human Epidermal Growth Factor Receptor 2 (ERBB2) Amplification Status: Clinical Validation in the Context of a Hybrid Capture-Based, Comprehensive Solid Tumor Genomic Profiling Assay. *J Mol Diagn*. 2017;19(2):244-254. doi:10.1016/j.jmoldx.2016.09.010.

4.Vicario R, Peg V, Morancho B, et al. Patterns of HER2 Gene Amplification and Response to Anti-HER2 Therapies. *PLoS ONE*. 2015;10(6):e0129876. doi:10.1371/journal.pone.0129876.

5.Hiatt JB, Pritchard CC, Salipante SJ, O'Roak BJ, Shendure J. Single molecule molecular inversion probes for targeted, high-accuracy

detection of low-frequency variation. *Genome Res*. 2013;23(5):843-854. doi:10.1101/gr.147686.112.

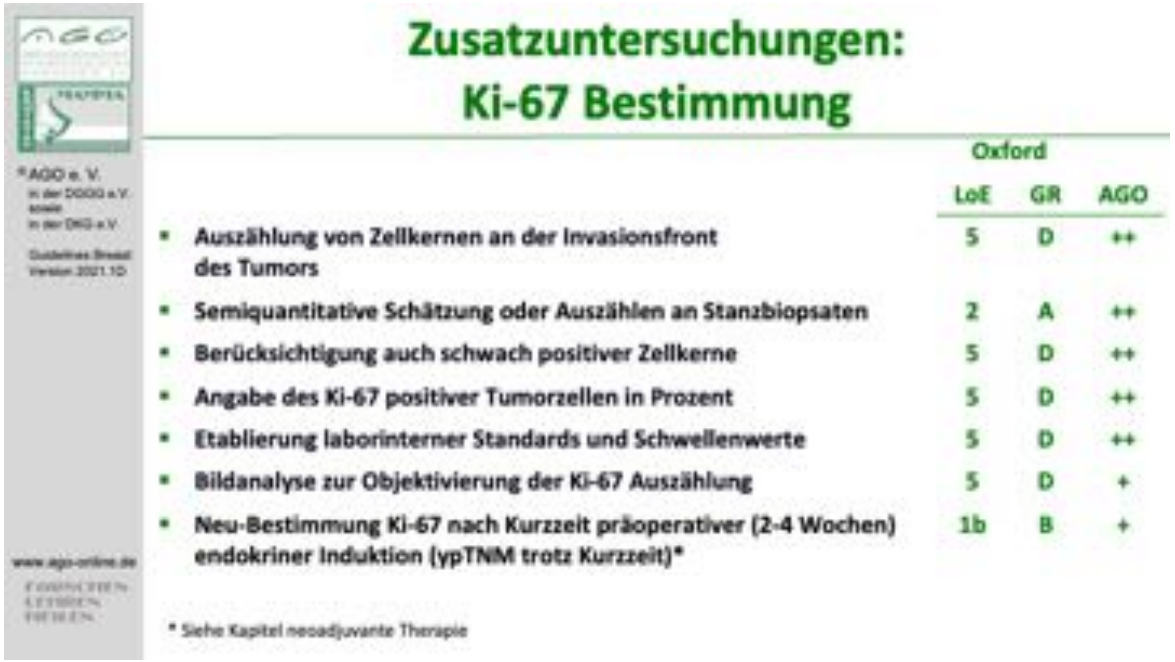
6. Christgen M, van Luttikhuizen JL, Raap M, et al. Precise ERBB2 copy number assessment in breast cancer by means of molecular inversion probe array analysis. *Oncotarget*. 2016;7(50):82733-82740. doi:10.18632/oncotarget.12421.

7.Christgen M, Harbeck N, Gluz O, Nitz U, Kreipe HH. Recognition and handling of discordant negative human epidermal growth factor receptor 2 classification by Oncotype DX in patients with breast cancer. *J Clin Oncol*. 2012;30(26):3313–4–authorreply3314–5. doi:10.1200/JCO.2012.42.1990.

8.Dabbs DJ, Klein ME, Mohsin SK, Tubbs RR, Shuai Y, Bhargava R. High false-negative rate of HER2 quantitative reverse transcription polymerase chain reaction of the Oncotype DX test: an independent quality assurance study. *J Clin Oncol*. 2011;29(32):4279-4285. doi:10.1200/JCO.2011.34.7963.

9.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.

10.Denkert C, Huober J, Loibl S, et al. HER2 and ESR1 mRNA expression levels and response to neoadjuvant trastuzumab plus chemotherapy in patients with primary breast cancer. *Breast Cancer Res*. 2013;15(1):R11. doi:10.1186/bcr3384.



<u>Ki-67 Methods and Reproducibility</u>

1.Leung SCY, Nielsen TO, Zabaglo L, et al. Analytical validation of a standardized scoring protocol for Ki67: phase 3 of an international multicenter collaboration. *npj Breast Cancer*. 2016;2:16014. doi:10.1038/npjbcancer.2016.14.

2.Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol. 2016 Jul 10;34(20):2341-9. doi: 10.1200/JCO.2015.63.5383

3.Hida AI, Bando K, Sugita A, et al. Visual assessment of Ki67 using a 5-grade scale (Eye-5) is easy and practical to classify breast cancer subtypes with high reproducibility. *SciMed Central*. 2015;68(5):356-361. doi:10.1136/jclinpath-2014-202695.

4.Vörös A, Csörgo E, Nyári T, Cserni G. An intra- and interobserver reproducibility analysis of the Ki-67 proliferation marker assessment on core biopsies of breast cancer patients and its potential clinical implications. *Pathobiology*. 2013;80(3):111-118. doi:10.1159/000343795.

5.Gudlaugsson E, Skaland I, Janssen EAM, et al. Comparison of the effect of different techniques for measurement of Ki67 proliferation on reproducibility and prognosis prediction accuracy in breast cancer. *Histopathology*. 2012;61(6):1134-1144. doi:10.1111/j.1365-2559.2012.04329.x.

6. Varga Z, Diebold J, Dommann-Scherrer C, et al. How reliable is Ki-67 immunohistochemistry in grade 2 breast carcinomas? A QA study of the Swiss Working Group of Breast- and Gynecopathologists. *PLoS ONE*. 2012;7(5):e37379. doi:10.1371/journal.pone.0037379.

7.Polley, M.-Y. C., Leung, S. C. Y., McShane, L. M., et al. (2013). An International Ki67 Reproducibility Study. Journal of the National Cancer Institute. doi:10.1093/jnci/djt306

8.Varga, Z., Diebold, J., Dommann-Scherrer, C., et al. (2012). How Reliable Is Ki-67 Immunohistochemistry in Grade 2 Breast Carcinomas? A QA Study of the Swiss Working Group of Breast- and Gynecopathologists. PloS One, 7(5), e37379. doi:10.1371/journal.pone.0037379.t003

9.Zabaglo, L., Salter, J., Anderson, H., et al. (2010). Comparative validation of the SP6 antibody to Ki67 in breast cancer. Journal of Clinical Pathology, 63(9), 800–804. doi:10.1136/jcp.2010.077578

Impact of Ki-67 staining

1.Tao M, Chen S, Zhang X, Zhou Q. Ki-67 labeling index is a predictive marker for a pathological complete response to neoadjuvant chemotherapy in breast cancer: A meta-analysis. 2017;96(51):e9384. doi:10.1097/MD.0000000000009384

2.Ignatiadis M, Azim HA, Desmedt C, et al. The Genomic Grade Assay Compared With Ki67 to Determine Risk of Distant Breast Cancer Recurrence. *JAMA Oncol*. 2016;2(2):217-224. doi:10.1001/jamaoncol.2015.4377.

3.Nitz, U., Gluz, O., Huober, J., et al. (2014). Final analysis of the prospective WSG-AGO EC-Doc versus FEC phase III trial in intermediate-risk (pN1) early breast cancer: efficacy and predictive value of Ki67 expression. Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO, 25(8), 1551–1557. doi:10.1093/annonc/mdu186

4.Inwald, E. C., Klinkhammer-Schalke, M., Hofstädter, F., et al. (2013). Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Research and Treatment, 139(2), 539–552. doi:10.1007/s10549-013-2560-8

5.Penault-Llorca, F, F Andre, C Sagan, et al. “Ki67 Expression and Docetaxel Efficacy in Patients with Estrogen Receptor-Positive Breast Cancer.” Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 27, no. 17 (June 8, 2009): 2809–15. doi:10.1200/JCO.2008.18.2808.

Ki-67 Image Analysis

1.Abubakar M, Orr N, Daley F, et al. Prognostic value of automated KI67 scoring in breast cancer: a centralised evaluation of 8088 patients from 10 study groups. *Breast Cancer Res*. 2016;18(1):104. doi:10.1186/s13058-016-0765-6.

2.Abubakar M, Howat WJ, Daley F, et al. High-throughput automated scoring of Ki67 in breast cancer tissue microarrays from the Breast Cancer Association Consortium. *J Pathol Clin Res*. 2016;2(3):138-153. doi:10.1002/cjp2.42.

3.Zhong F, Bi R, Yu B, Yang F, Yang W, Shui R. A Comparison of Visual Assessment and Automated Digital Image Analysis of Ki67 Labeling Index in Breast Cancer. *PLoS ONE*. 2016;11(2):e0150505. doi:10.1371/journal.pone.0150505.

4.Klauschen F, Wienert S, Schmitt WD, et al. Standardized Ki67 Diagnostics Using Automated Scoring--Clinical Validation in the GeparTrio Breast Cancer Study. *Clin Cancer Res*. 2015;21(16):3651-3657. doi:10.1158/1078-0432.CCR-14-1283.

5.Christgen M, Ahsen von S, Christgen H, Länger F, Kreipe H. The region-of-interest size impacts on Ki67 quantification by computer-assisted image analysis in breast cancer. *Hum Pathol*. 2015;46(9):1341-1349. doi:10.1016/j.humpath.2015.05.016.

6.Di Cataldo S, Ficarra E, Macii E. Computer-aided techniques for chromogenic immunohistochemistry: status and directions. *Comput Biol Med*. 2012;42(10):1012-1025. doi:10.1016/j.compbiomed.2012.08.004.

7.Mohammed ZMA, McMillan DC, Elsberger B, et al. Comparison of visual and automated assessment of Ki-67 proliferative activity and their impact on outcome in primary operable invasive ductal breast cancer. *Br J Cancer*. 2012;106(2):383-388. doi:10.1038/bjc.2011.569.

8.Gudlaugsson, E., Skaland, I., Janssen, E. A. M., et al. (2012). Comparison of the effect of different techniques for measurement of Ki67 proliferation on reproducibility and prognosis prediction accuracy in breast cancer. Histopathology, 61(6), 1134–1144. doi:10.1111/j.1365-2559.2012.04329.x

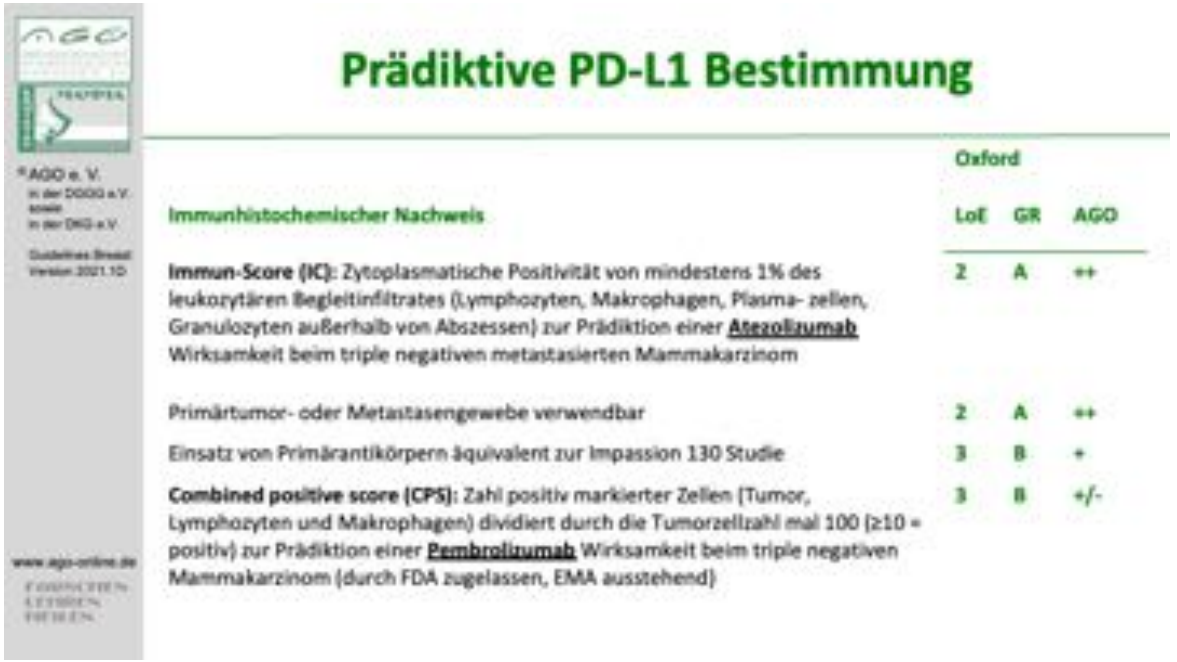
9.Konsti J, Lundin M, Joensuu H, et al. Development and evaluation of a virtual microscopy application for automated assessment of Ki-67 expression in breast cancer. *BMC Clin Pathol*. 2011;11(1):3. doi:10.1186/1472-6890-11-3.

Ki67 als dynamischer Marker nach Kurzzeit endokriner Therapie

1. Dowsett M, Ellis MJ, Dixon JM, Gluz Oet al. Evidence-based guidelines for managing patients with primary ER+ HER2- breast cancer deferred from surgery due to the COVID-19 pandemic. NPJ Breast Cancer. 2020 Jun 8;6:21.

2.Hofmann D, Nitz U, Gluz O, et al. WSG ADAPT - adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: Study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator-initiated phase II/III trial. Trials. 2013;14:261-6215-14-261.

3.Smith IE, Robertson J, Kilburn L, et al. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone sensitive early breast cancer:The POETIC randomised trial. Lancet Oncology. 2020.



Prädiktive PD-L1 Bestimmung

Immunhistochemischer Nachweis	Oxford LoE	Oxford GR	AGO
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	2	A	++
Primärtumor- oder Metastasengewebe verwendbar	2	A	++
Einsatz von Primärantikörpern äquivalent zur Impassion 130 Studie	3	B	+
Combined positive score (CPS): Zahl positiv markierter Zellen (Tumor, Lymphozyten und Makrophagen) dividiert durch die Tumorzellzahl mal 100 (≥10 = positiv) zur Prädiktion einer **Pembrolizumab** Wirksamkeit beim triple negativen Mammakarzinom (durch FDA zugelassen, EMA ausstehend)	3	B	+/-

1. Noske A, Ammann JU, Wagner DC, et al. A multicentre analytical comparison study of inter-reader and inter-assay agreement of four programmed death-ligand 1 immunohistochemistry assays for scoring in triple-negative breast cancer. *Histopathology*. September 2020. doi:10.1111/his.14254.
2. Rugo HS, Loi S, Adams S, et al. Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): Post-hoc analysis of IMpassion130. In: Vol 30. 2019:v858-v859. doi:10.1093/annonc/mdz394.009.
3. Arora S, Velichinskii R, Lesh RW, et al. Existing and Emerging Biomarkers for Immune Checkpoint Immunotherapy in Solid Tumors. *Adv Ther*. 2019;36(10):2638-2678. doi:10.1007/s12325-019-01051-z.
4. Torlakovic E, Lim HJ, Adam J, et al. "Interchangeability" of PD-L1 immunohistochemistry assays: a meta-analysis of diagnostic accuracy. *Mod Pathol*. 2019;18(2):312-314. doi:10.1038/s41379-019-0327-4.
5. Emens, L. A., Cruz, C., Eder, J. P., et al. (2018). Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. *JAMA Oncology*. http://doi.org/10.1001/jamaoncol.2018.4224
6. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018;379(22):2108-2121. doi:10.1056/NEJMoa1809615.

7. Schildhaus HU. Der prädiktive Wert der PD-L1-Diagnostik. *Der Pathologe*. 2018;39(6):498-519. doi:10.1007/s00292-018-0507-x.
8. Nixon, M. J., & Balko, J. M. (2018). Biomarkers for assessing the effectiveness of immunotherapy in breast cancer. *Biomarkers in Medicine*, *12*(2), 97–100. http://doi.org/10.2217/bmm-2017-0408
9. Goodman AM, Piccioni D, Kato S, et al. Prevalence of PDL1 Amplification and Preliminary Response to Immune Checkpoint Blockade in Solid Tumors. *JAMA Oncol*. 2018;4(9):1237-1244. doi:10.1001/jamaoncol.2018.1701.
10. Goodman AM, Piccioni D, Kato S, et al. Prevalence of PDL1 Amplification and Preliminary Response to Immune Checkpoint Blockade in Solid Tumors. *JAMA Oncol*. 2018;4(9):1237-1244. doi:10.1001/jamaoncol.2018.1701.
11. Scheel AH, Baenfer G, Baretton G, et al. Interlaboratory concordance of PD-L1 immunohistochemistry for non-small-cell lung cancer. *Histopathology*. 2018;72(3):449-459. doi:10.1111/his.13375.
12. Rehman JA, Han G, Carvajal-Hausdorf DE, et al. Quantitative and pathologist-read comparison of the heterogeneity of programmed death-ligand 1 (PD-L1) expression in non-small cell lung cancer. *Mod Pathol*. 2017;30(3):340-349. doi:10.1038/modpathol.2016.186.
13. Scheel AH, Dietel M, Heukamp LC, et al. Prädiktive PD-L1-Immunhistochemie beim nichtkleinzelligen Bronchialkarzinom : Aktueller Stand und Erfahrungen der ersten deutschen Harmonisierungsstudie. *Der Pathologe*. 2016;37(6):557-567. doi:10.1007/s00292-016-0189-1.
14. Scheel AH, Dietel M, Heukamp LC, et al. Harmonized PD-L1 immunohistochemistry for pulmonary squamous-cell and adenocarcinomas. *Mod Pathol*. 2016;29(10):1165-1172. doi:10.1038/modpathol.2016.117.

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	+

BRCA 1/2

1.Robson M, Im S-A, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med*. 2017;377(6):523-533. doi:10.1056/NEJMoa1706450.

2.Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33(3):244-250. doi:10.1200/JCO.2014.56.2728.

3.Davies H, Glodzik D, Morganella S, et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. *Nat Med*. 2017;83:1301. doi:10.1038/nm.4292.

4.Gross E, van Tinteren H, Li Z, et al. Identification of BRCA1-like triple-negative breast cancers by quantitative multiplex-ligation-dependent probe amplification (MLPA) analysis of BRCA1-associated chromosomal regions: a validation study. *BMC Cancer*. 2016;16(1):811. doi:10.1186/s12885-016-2848-2.

5.Telli ML, Timms KM, Reid J, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. *Clin Cancer Res*. 2016;22(15):3764-3773. doi:10.1158/1078-0432.CCR-15-2477.

6.Petrillo M, Nero C, Amadio G, Gallo D, Fagotti A, Scambia G. Targeting the hallmarks of ovarian cancer: The big picture. *Gynecologic Oncology*. 2016;142(1):176-183. doi:10.1016/j.ygyno.2016.03.037.

7. Azzollini J, Scuvera G, Bruno E, et al. Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study. *Eur J Intern Med*. 2016;32:65-71. doi:10.1016/j.ejim.2016.03.010.

8.De Picciotto N, Cacheux W, Roth A, Chappuis PO, Labidi-Galy SI. Ovarian cancer: Status of homologous recombination pathway as a predictor of drug response. *Critical Reviews in Oncology/Hematology*. 2016;101:50-59. doi:10.1016/j.critrevonc.2016.02.014.

9.Lord CJ, Ashworth A. BRCAness revisited. *Nat Rev Cancer*. 2016;16(2):110-120. doi:10.1038/nrc.2015.21.

PIK3CA

1.André F, Ciruelos E, Rubovszky G, Campone M et al. (2019) Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 380:1929-1940. doi: 10.1056/NEJMoa1813904

2.Luen SJ, Asher R, Lee CK, et al. Association of Somatic Driver Alterations With Prognosis in Postmenopausal, Hormone Receptor-Positive, HER2-Negative Early Breast Cancer: A Secondary Analysis of the BIG 1-98 Randomized Clinical Trial. *JAMA Oncol*. 2018;4(10):1335-1343. doi:10.1001/jamaoncol.2018.1778.

3.Stearns V, Park BH. PIK3CA Mutations in Hormone Receptor-Positive Breast Cancers: PIKing Biomarkers to Inform Adjuvant Endocrine Therapy Decisions. *JAMA Oncol*. 2018;4(10):1330-1332. doi:10.1001/jamaoncol.2018.1766.

4.Lasota J, Felisiak-Golabek A, Wasąg B, et al. Frequency and clinicopathologic profile of PIK3CA mutant GISTs: molecular genetic study of 529 cases. *Mod Pathol*. 2016;29(3):275-282. doi:10.1038/modpathol.2015.160.

5.Wilson TR, Yu J, Lu X, et al. The molecular landscape of high-risk early breast cancer: comprehensive biomarker analysis of a phase III adjuvant population. *npj Breast Cancer*. 2016;2(1):16022. doi:10.1038/npjbcancer.2016.22.

6.Bosch A, Li Z, Bergamaschi A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci Transl Med*. 2015;7(283):283ra51-283ra51. doi:10.1126/scitranslmed.aaa4442.

7.Papaxoinis G, Kotoula V, Alexopoulou Z, et al. Significance of PIK3CA Mutations in Patients with Early Breast Cancer Treated with Adjuvant Chemotherapy: A Hellenic Cooperative Oncology Group (HeCOG) Study. *PLoS ONE*. 2015;10(10):e0140293. doi:10.1371/journal.pone.0140293.

8.Baselga J, Cortés J, Im S-A, et al. Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in human epidermal growth factor receptor 2-positive, first-line metastatic breast cancer. *J Clin Oncol*. 2014;32(33):3753-3761.

doi:10.1200/JCO.2013.54.5384.

9. Henry NL, Schott AF, Hayes DF. Assessment of PIK3CA mutations in human epidermal growth factor receptor 2-positive breast cancer: clinical validity but not utility. *J Clin Oncol*. 2014;32(29):3207-3209. doi:10.1200/JCO.2014.57.6132.

10.André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). *Lancet Oncol*. 2014;15(3):267-274. doi:10.1016/S1470-2045(13)70611-9.

11.Tandon M, Chen Z, Pratap J. Runx2 activates PI3K/Akt signaling via mTORC2 regulation in invasive breast cancer cells. *Breast Cancer Res*. 2014;16(1):R16. doi:10.1186/bcr3611.

12.Lehmann BD, Bauer JA, Schafer JM, et al. PIK3CA mutations in androgen receptor-positive triple negative breast cancer confer sensitivity to the combination of PI3K and androgen receptor inhibitors. *Breast Cancer Res*. 2014;16(4):406. doi:10.1186/s13058-014-0406-x.

13.Cizkova M, Dujaric M-E, Lehmann-Che J, et al. Outcome impact of PIK3CA mutations in HER2-positive breast cancer patients treated with trastuzumab. *Br J Cancer*. 2013;108(9):1807-1809. doi:10.1038/bjc.2013.164.

14.Vinayak S, Carlson RW. mTOR inhibitors in the treatment of breast cancer. *Oncology (Williston Park, NY)*. 2013;27(1):1-13

HER2-Mutation

1.Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature*. 2018;554(7691):189-194. doi:10.1038/nature25475.

2.Ma CX, Bose R, Gao F, et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. *Clin Cancer Res*. 2017;23(19):5687-5695. doi:10.1158/1078-0432.CCR-17-0900.

3.Petrelli F, Tomasello G, Barni S, et al.: Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. *Breast Cancer Res Treat*. 2017;166(2):339-349. doi:10.1007/s10549-017-4419-x.

4.Ross JS, Gay LM, Wang K, et al. Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: An emerging opportunity for anti-HER2 targeted therapies. *Cancer*. 2016;122(17):2654-2662. doi:10.1002/cncr.30102.

5.Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov*.

2013;3(2):224-237. doi:10.1158/2159-8290.CD-12-0349.

6. Weigelt B, Reis-Filho JS. Activating mutations in HER2: neu opportunities and neu challenges. *Cancer Discov*. 2013;3(2):145-147. doi:10.1158/2159-8290.CD-12-0585.

7.Herter-Sprie GS, Greulich H, Wong K-K. Activating Mutations in ERBB2 and Their Impact on Diagnostics and Treatment. *Front Oncol*. 2013;3:86. doi:10.3389/fonc.2013.00086.

8.Greulich H, Kaplan B, Mertins P, et al. Functional analysis of receptor tyrosine kinase mutations in lung cancer identifies oncogenic extracellular domain mutations of ERBB2. *Proc Natl Acad Sci U S A*. 2012;109(36):14476-14481. doi:10.1073/pnas.1203201109.

9.Zito CI, Riches D, Kolmakova J, Simons J, Egholm M, Stern DF. Direct resequencing of the complete ERBB2 coding sequence reveals an absence of activating mutations in ERBB2 amplified breast cancer. *Genes Chromosomes Cancer*. 2008;47(7):633-638. doi:10.1002/gcc.20566.

10.Lee JW, Soung YH, Seo SH, et al. Somatic mutations of ERBB2 kinase domain in gastric, colorectal, and breast carcinomas. *Clin Cancer Res*. 2006;12(1):57-61. doi:10.1158/1078-0432.CCR-05-0976.

ESR1

1.Dustin D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. *Cancer*. 2019;125(21):3714-3728. doi:10.1002/cncr.32345.

2.Fribbens C, Garcia Murillas I, Beaney M, et al. Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. *Ann Oncol*. 2018;29(1):145-153. doi:10.1093/annonc/mdx483.

3.Jeselsohn R, Bergholz JS, Pun M, et al. Allele-Specific Chromatin Recruitment and Therapeutic Vulnerabilities of ESR1 Activating Mutations. *Cancer Cell*. 2018;33(2):173-186.e175. doi:10.1016/j.ccell.2018.01.004.

4.Bartels S, Christgen M, Luft A, et al. Estrogen receptor (ESR1) mutation in bone metastases from breast cancer. *Mod Pathol*. 2018;31(1):56-61. doi:10.1038/modpathol.2017.95.

5.Toy W, Weir H, Razavi P, et al. Activating ESR1 Mutations Differentially Affect the Efficacy of ER Antagonists. *Cancer Discov*. 2017;7(3):277-287. doi:10.1158/2159-8290.CD-15-1523.

6.Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. *J Clin Oncol*. 2016;34(25):2961-2968. doi:10.1200/JCO.2016.67.3061.

7. Chandarlapaty S, Chen D, He W, et al. Prevalence of ESR1 Mutations in Cell-Free DNA and Outcomes in Metastatic Breast Cancer: A Secondary Analysis of the BOLERO-2 Clinical Trial. *JAMA Oncol*. 2016;2(10):1310-1315. doi:10.1001/jamaoncol.2016.1279.

8.Jeselsohn R, Yelensky R, Buchwalter G, et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor-positive breast cancer. *Clin Cancer Res*. 2014;20(7):1757-1767. doi:10.1158/1078-0432.CCR-13-2332.

9.Segal CV, Dowsett M. Estrogen receptor mutations in breast cancer--new focus on an old target. *Clin Cancer Res*. 2014;20(7):1724-1726. doi:10.1158/1078-0432.CCR-14-0067.

10.Giguère V. Estrogen receptor mutations in breast cancer-an anticipated "rediscovery?". *Mol Endocrinol*. 2014;28(4):427-428. doi:10.1210/me.2014-1071.

11.Fuqua SAW, Gu G, Rechoum Y. Estrogen receptor (ER) α mutations in breast cancer: hidden in plain sight. *Breast Cancer Res Treat*. 2014;144(1):11-19. doi:10.1007/s10549-014-2847-4.

NTRK

1.Remoué A, Conan-Charlet V, Bourhis A, et al. Non-secretory breast carcinomas lack NTRK rearrangements and TRK protein expression. *Pathol Int*. 2019;69(2):94-96. doi:10.1111/pin.12766.

2.Ricciuti B, Genova C, Crinò L, Libra M, Leonardi GC. Antitumor activity of larotrectinib in tumors harboring NTRK gene fusions: a short review on the current evidence. *Onco Targets Ther*. 2019;12:3171-3179. doi:10.2147/OTT.S177051.

3.Condorelli R, Mosele F, Verret B, et al. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2019;30(3):365-373. doi:10.1093/annonc/mdz036.

4.Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0.

5.Pfarr N, Kirchner M, Lehmann U, et al. Testing NTRK testing: Wet-lab and in silico comparison of RNA-based targeted sequencing assays. *Genes Chromosomes Cancer*. 2020;59(3):178-188. doi:10.1002/gcc.22819.

6.Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747. doi:10.1038/s41571-018-0113-0.

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

1.Cortes-Ciriano I, Lee S, Park W-Y, Kim TM, Park PJ. A molecular portrait of microsatellite instability across multiple cancers. *Nature Communications*. 2017;8:15180. doi:10.1038/ncomms15180.

2.Win AK, Lindor NM, Jenkins MA. Risk of breast cancer in Lynch syndrome: a systematic review. *Breast Cancer Res*. 2013;15(2):R27. doi:10.1186/bcr3405.

3.Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol*. 2012;30(35):4409-4415. doi:10.1200/JCO.2012.43.2278.