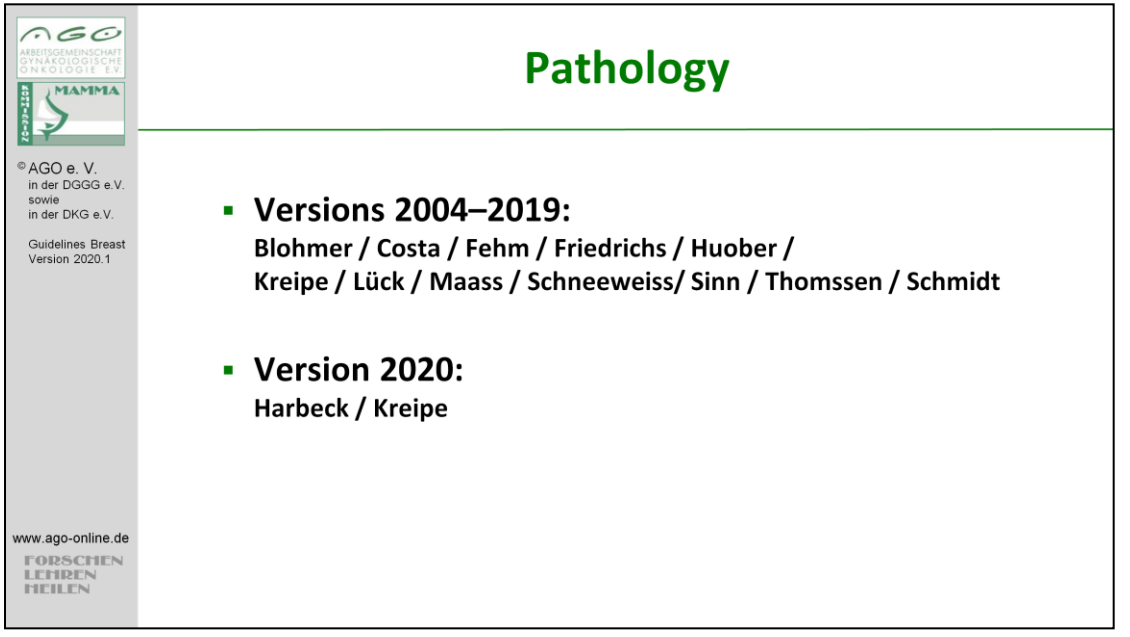
Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
Version 2020.1

Pathology



Screened data bases: PubMed 2019.

Search Query:

(Breast Diseases/PA[mh] AND ("2018/01/01"[dp] : "2019/01/01"[dp]) AND ("english"[la] OR "german"[la])

Guidelines screened

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2017
- NCCN Breast cancer V.I.2014Cochrane: Decision aids for risk communication update 2009
- EUSOMA position paper: Diagnosis of breast disease
- Royal College of Pathologists & NHS Breast Screening Programme, Pathology Reporting of Breast Disease, January 2005
- European guidelines for quality assurance in breast cancer screening and diagnosis 4th Edition

1. Arbeitsgruppe Qualitätssicherung Pathologie in der konzertierten Aktion zur Brustkrebsfrüherkennung in Deutschland (2002).

Anleitung Mammapathologie.

2. Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland 2008. http://www.senologie.org/download/pdf/s3_brustkrebsfrueherkennung_2008.pdf
3. Association of Directors of Anatomic and Surgical Pathology (1996). Recommendations for the reporting of breast carcinoma. Mod Pathol. 1996 Jan;9(1):77-81.
4. Deutsche Krebsgesellschaft und beteiligte medizinisch-wissenschaftliche Fachgesellschaften (2008). Interdisziplinäre Leitlinie Diagnose und Therapie des Mammakarzinoms der Frau. http://www.senologie.org/download/pdf/s3_ll_mammaca_11_02_2008.pdf
5. Lester SC, Bose S, Chen YY, et al: Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009 Oct;133(10):1515-38.
6. Reiner-Concin, S. Lax. Mammakarzinom Pathologie. In: Manual der gynäkologischen Onkologie. Arbeitsgemeinschaft für gynäkologische Onkologie (AGO) der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG) A. Reinthaller, L. Hefler (Hrsg.) http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/
7. Schweizerische Gesellschaft für Pathologie (2002). Leitlinien zur Sicherung und Förderung der Qualitätskontrolle. http://www.sgpath.ch
8. 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
9. Royal College of Pathologists (UK) (2005). NHSBSP guidelines for pathology reporting in breast disease. http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html
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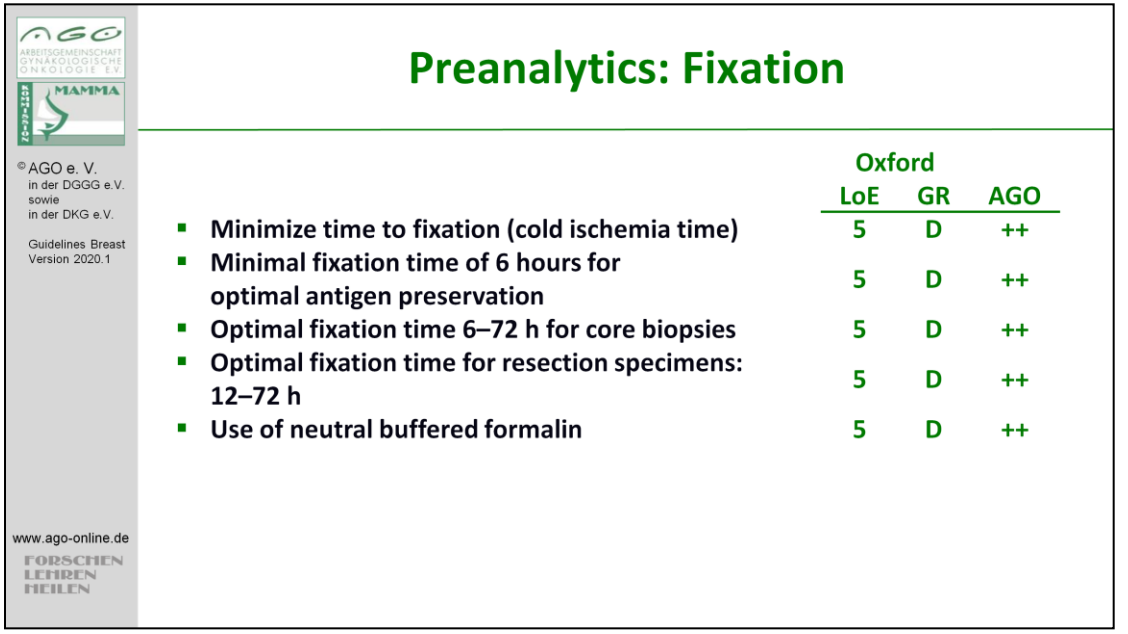

Antigen preservation

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
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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.
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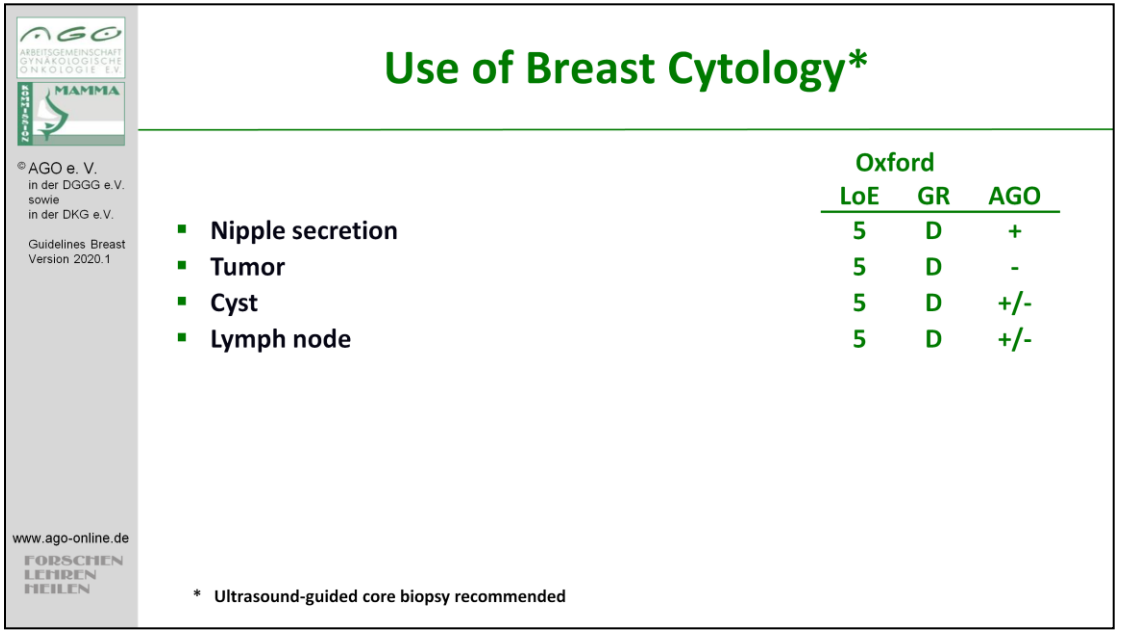

1. Day, C, N Moatamed, AM Fimbres, et al: A Retrospective Study of the Diagnostic Accuracy of Fine-Needle Aspiration for Breast Lesions and Implications for Future Use. Diagnostic Cytopathology 36, no. 12 (November 30, 2008): 855–60.
2. Pinder, S E, and J S Reis-Filho. Non-Operative Breast Pathology. 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.
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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
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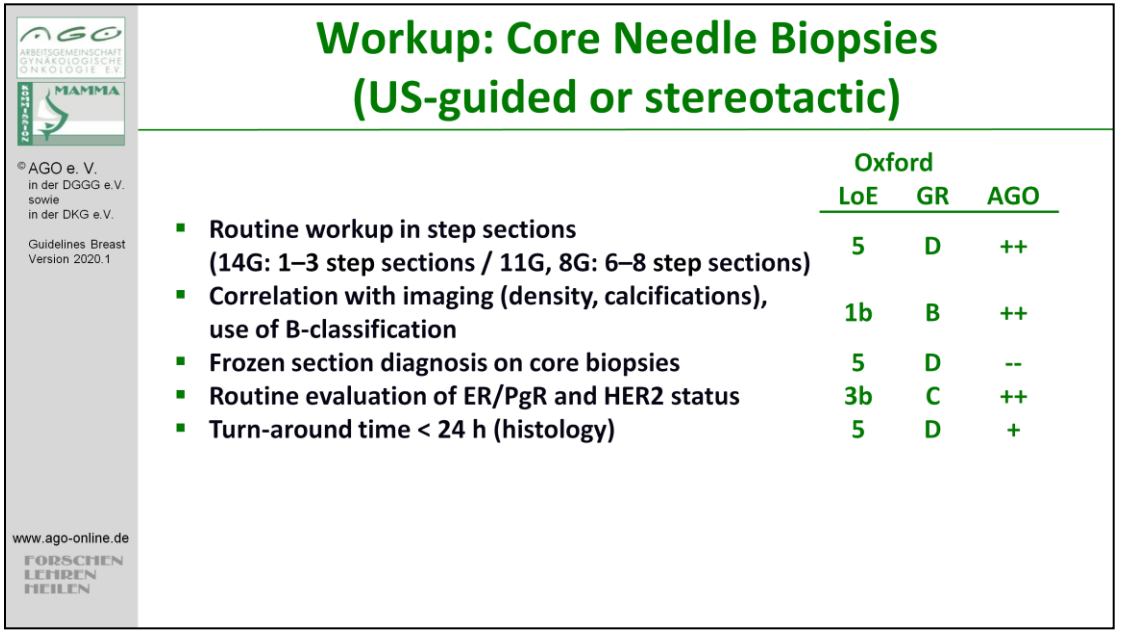
needle aspiration cytology correlation. *Journal of Cancer Research and Therapeutics*, *14*(5), 1071–1074. http://doi.org/10.4103/0973-1482.191053



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

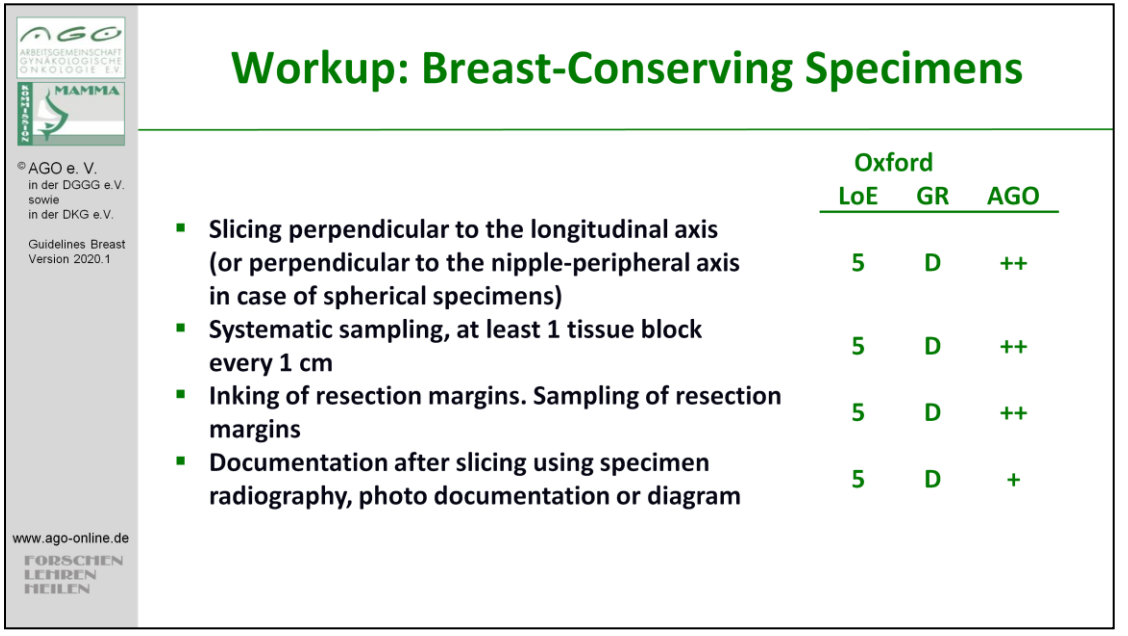
1. Lebeau, Gerber, Brucker et al. (2017): Pathomorphologische Untersuchung. In: AWMF: S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, S. 100 - 139.
2. Dämmrich, M., Thomssen, C., Hillemanns, P. et al. (2012). Intraoperative pathologische Sofortuntersuchung in der Mammachirurgie. *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



1. Sinn HP, Anton HW, Magener A, et al. Extensive and predominant in situ component in breast carcinoma: their influence on treatment results after breast-conserving therapy. Eur J Cancer. 1998 Apr;34(5):646-53.
2. Connolly JL, Boyages J, Nixon AJ et al. Predictors of breast recurrence after conservative surgery and radiation therapy for invasive breast cancer. Mod Pathol. 1998;11:134-139.
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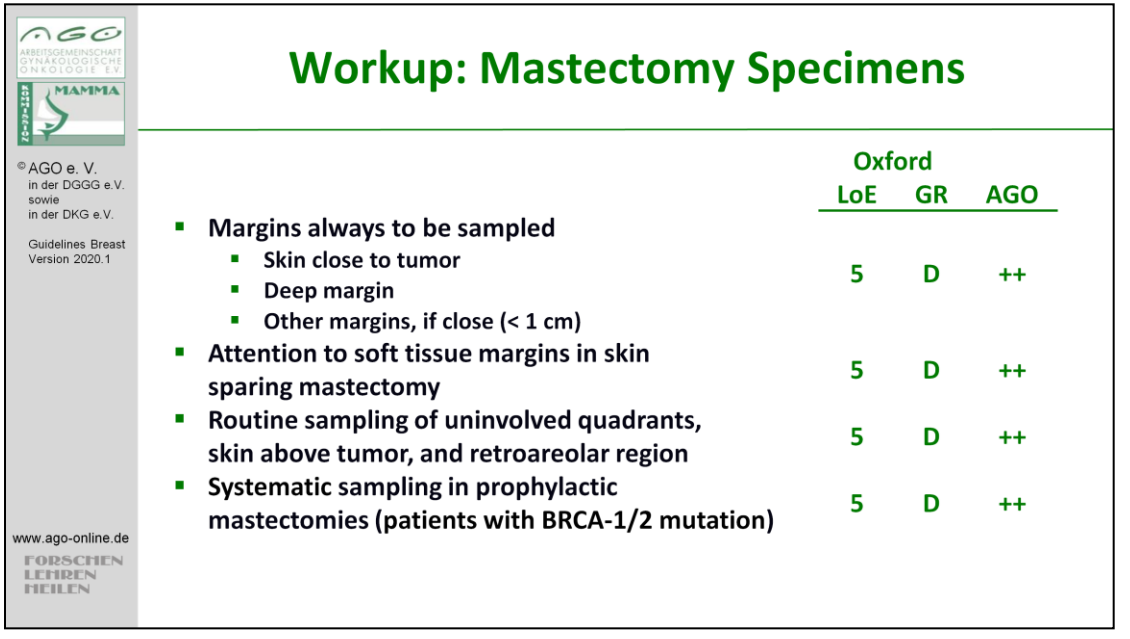

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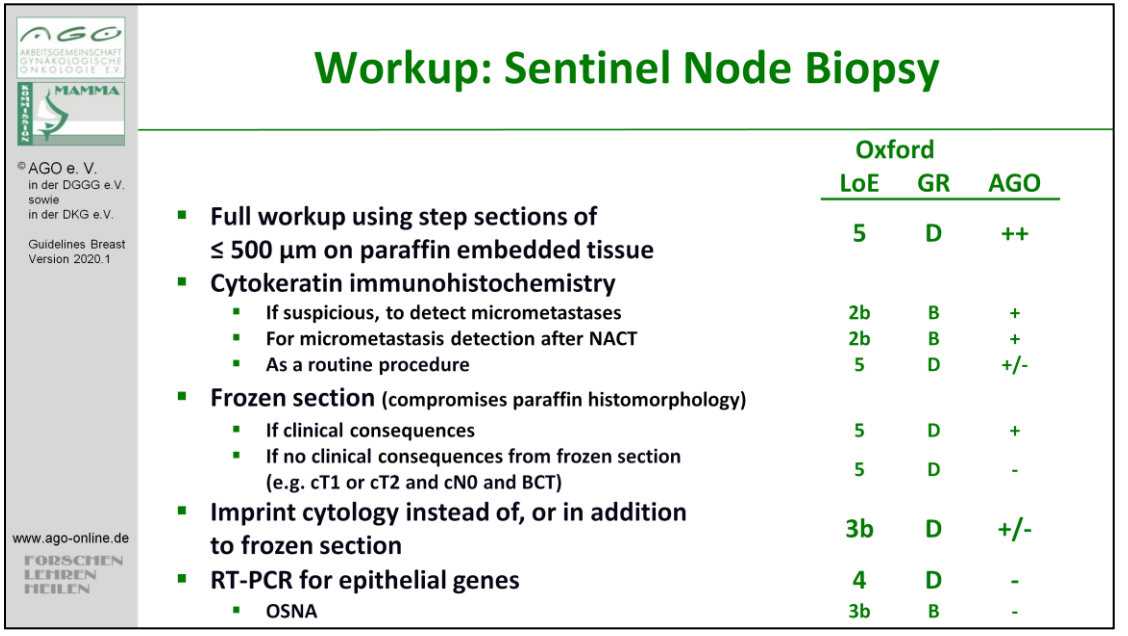


Statement: Evaluation of sentinel node biopsy

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

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

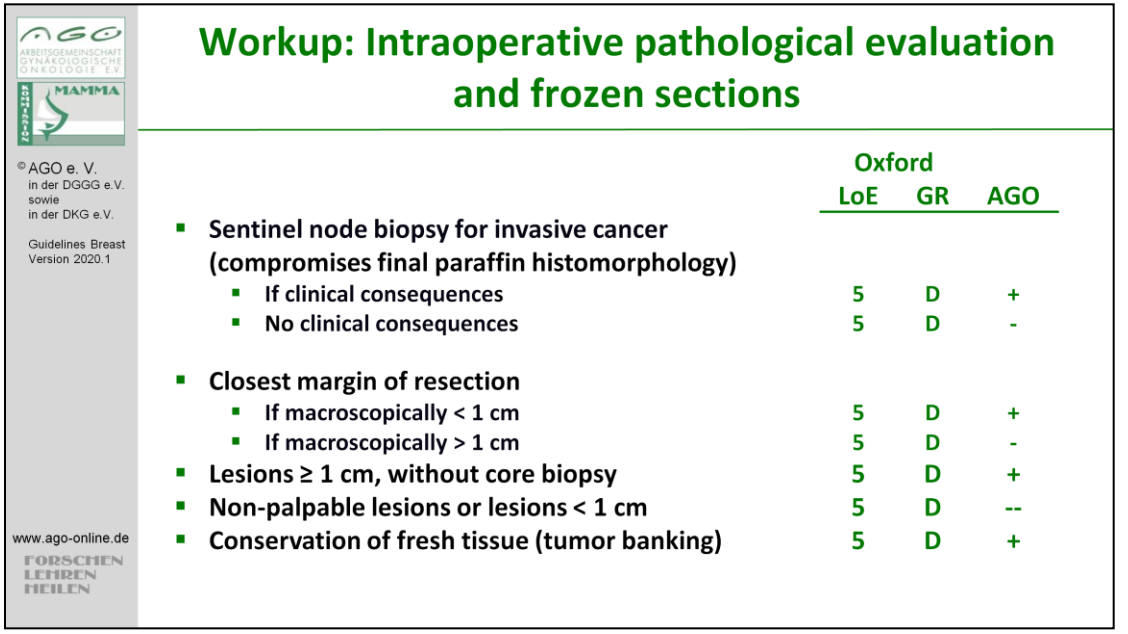
1. Langer, I., Guller, U., Berclaz, G. et al. (2009). Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study. *Breast Cancer Research and Treatment*, *113*(1), 129–136. http://doi.org/10.1007/s10549-008-9911-x

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

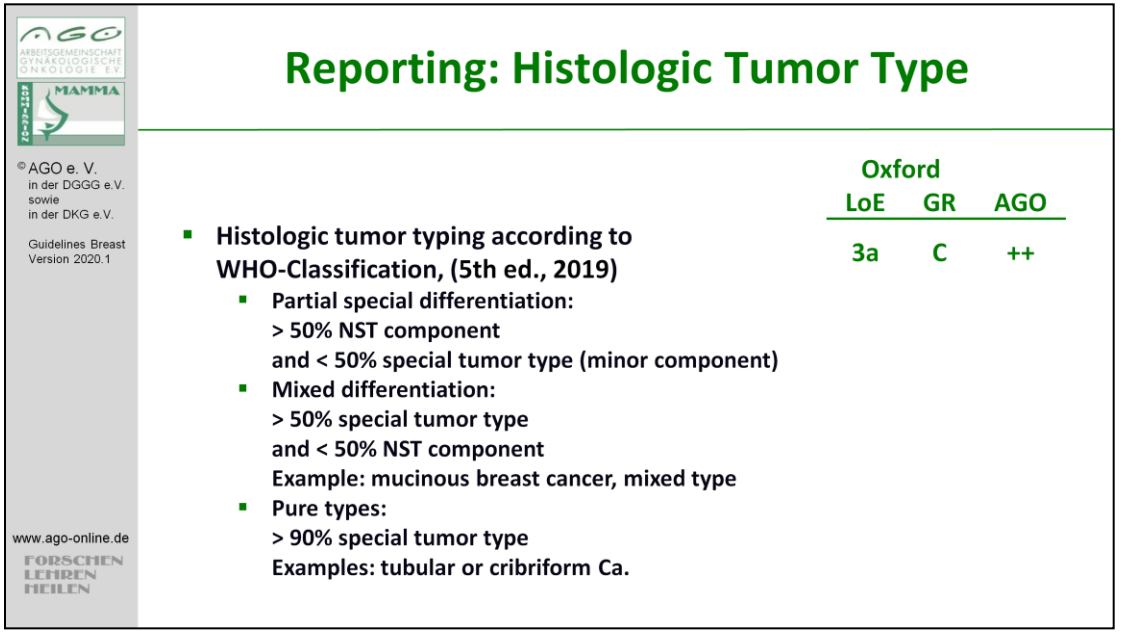
1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthaler R, Helfer L, Hrsg.). http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/
2. Kraus-Tiefenbacher U, Scheda A, Steil V, et al.Intraoperative radiotherapy (IORT) for breast cancer using the Intrabeam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

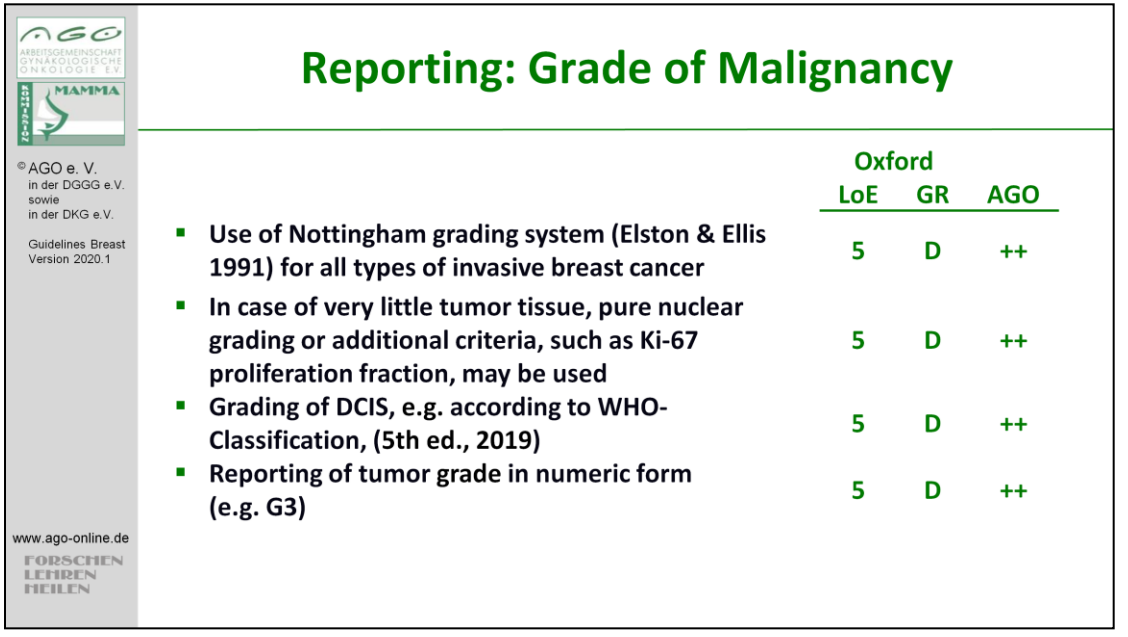
Statement: Non-palpable lesions or lesions < 1 cm

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: 256-27



WHO-Classification

1. Lebeau, A., Kriegsmann, M., Burandt, E., et al (2014). Invasive Mammakarzinome: Die aktuelle WHO classification. Der Pathologe, 35(1), 7–17.
2. Lakhani SR, Ellis I, Schnitt S et al. (2012) WHO Classification of Tumours of the Breast. IARC Press, Lyon
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

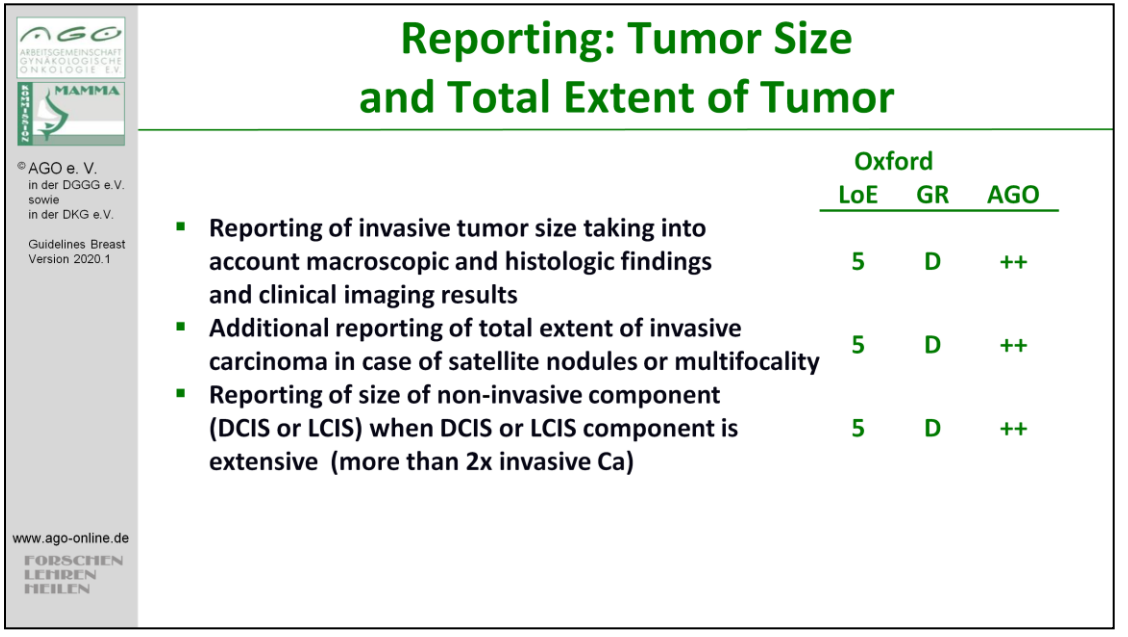


Grading

1. Elston, C., & Ellis, I. (1991). 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, 19(5), 403–410.
2. Lakhani SR, Ellis I, Schnitt S et al. (2012) WHO Classification of Tumours of the Breast. IARC Press, Lyon
3. Rakha, E. A., Reis-Filho, J. S., Baehner, F., et al. (2010). Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Research : BCR, 12(4), 207.
4. Rakha, E. A., El-Sayed, M. E., Lee, A. H. S. et al. (2008). Prognostic Significance of Nottingham Histologic Grade in Invasive Breast Carcinoma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 26(19), 3153–3158

Grading of invasive lobular carcinoma

1. Rakha, E. A., El-Sayed, M. E., Menon, S., et al. (2007). Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. Breast Cancer Research and Treatment, 111(1), 121–127.



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.

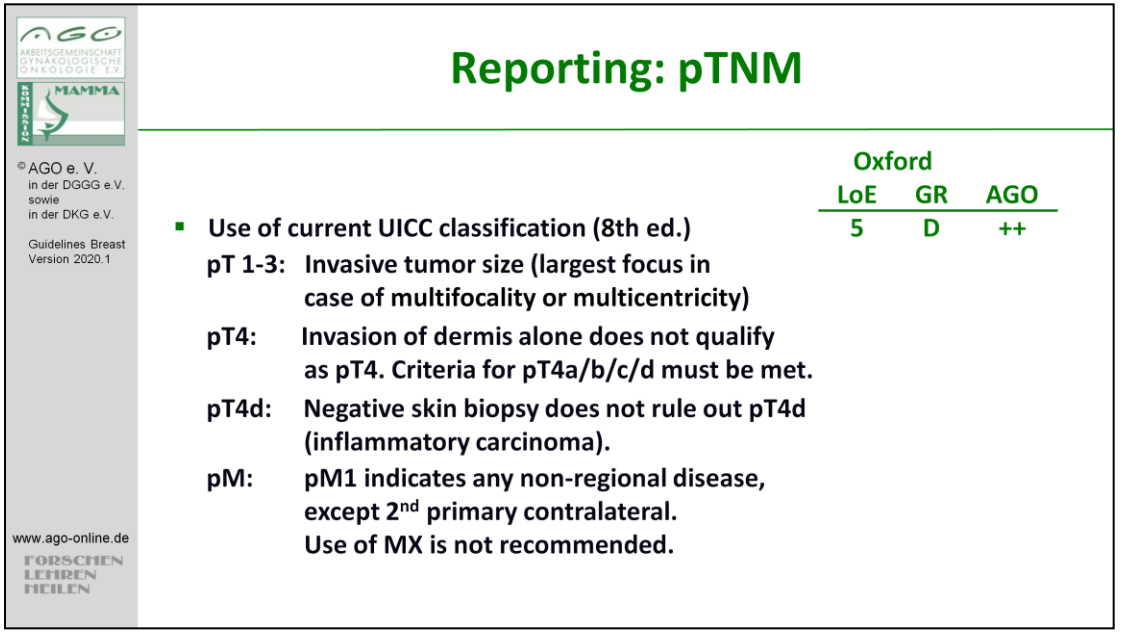
Multifocality

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. UICC (2010) TNM: Klassifikation maligner Tumoren. 7. Aufl. Wiley-VCH Verlag GmbH
2. American-Joint-Committee-on-Cancer (2010) AJCC cancer staging manual. Springer, New York; London

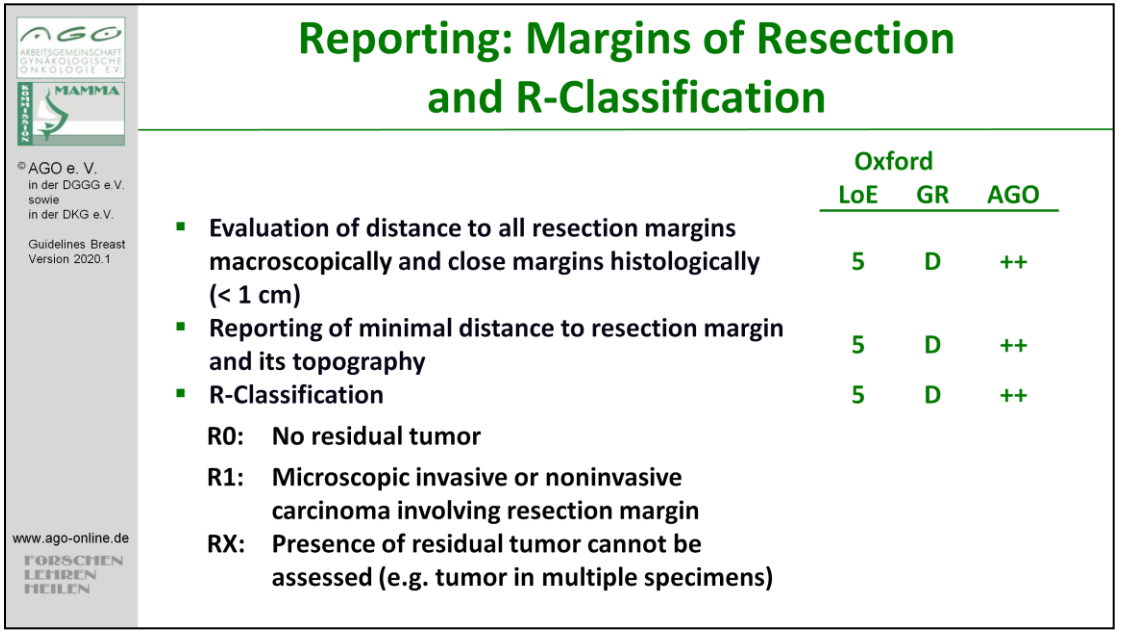
pT4b category: Involvemant of the skin

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. 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
2. 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.
3. 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
4. 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.
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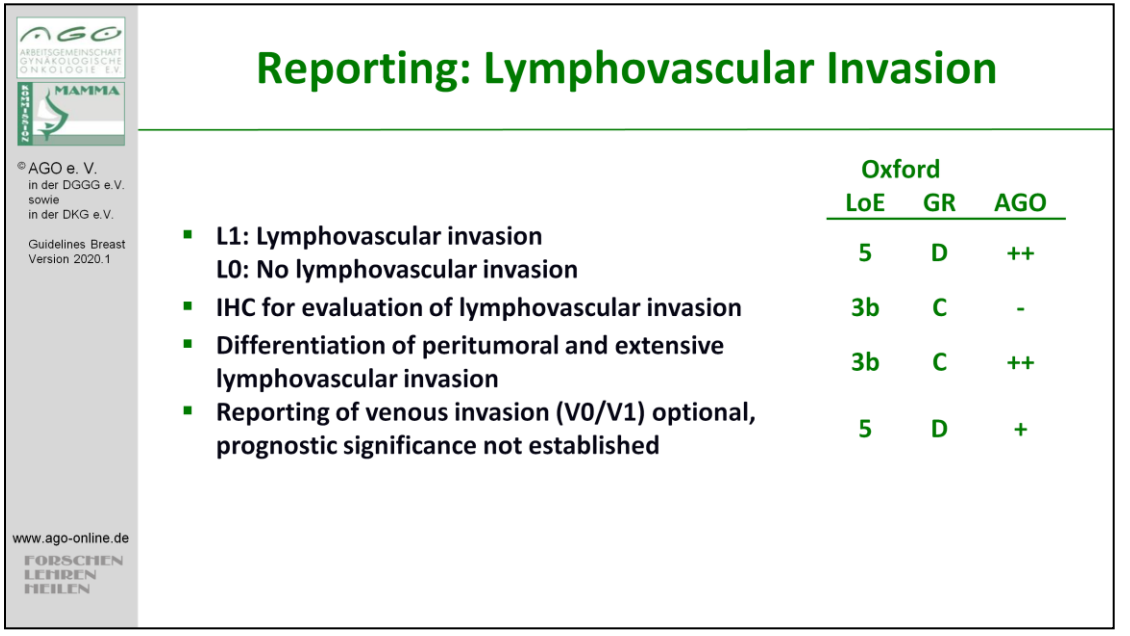
R-Classifikation

1. UICC (2010) TNM: Klassifikation maligner Tumoren. 7. Aufl. Wiley-VCH Verlag GmbH



Definition of L- and V-Classification

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Detection of angioinvasion

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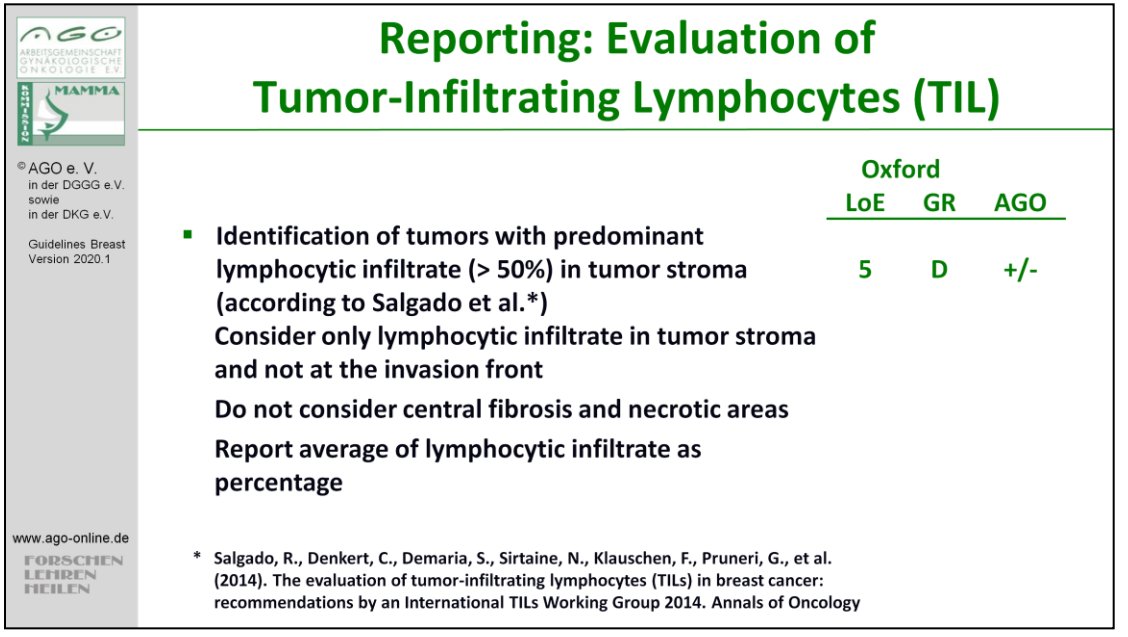

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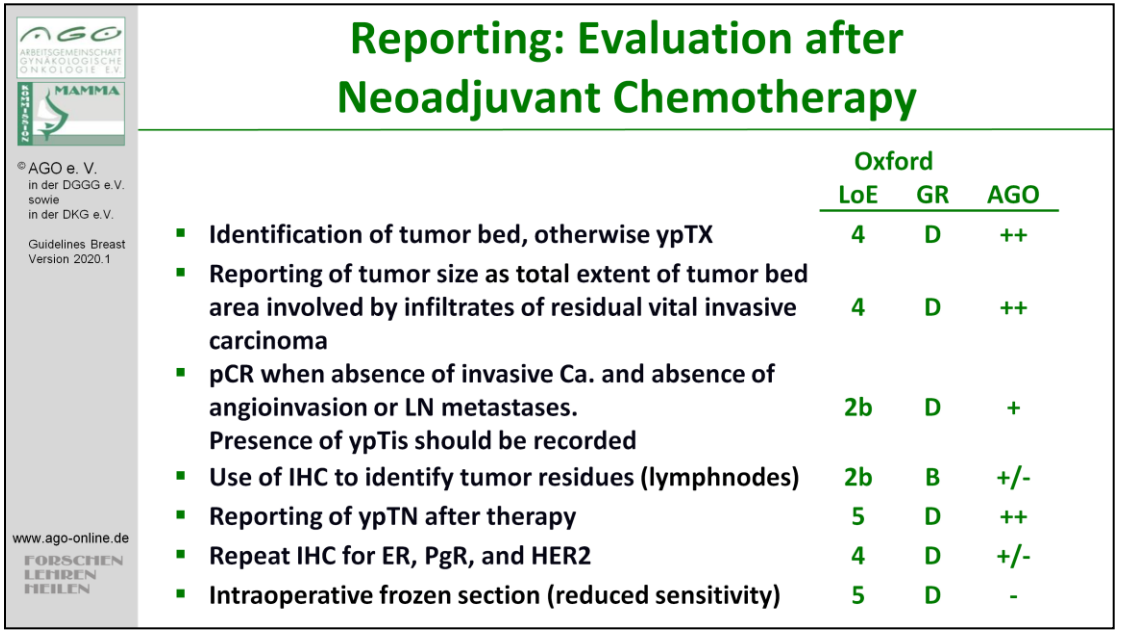

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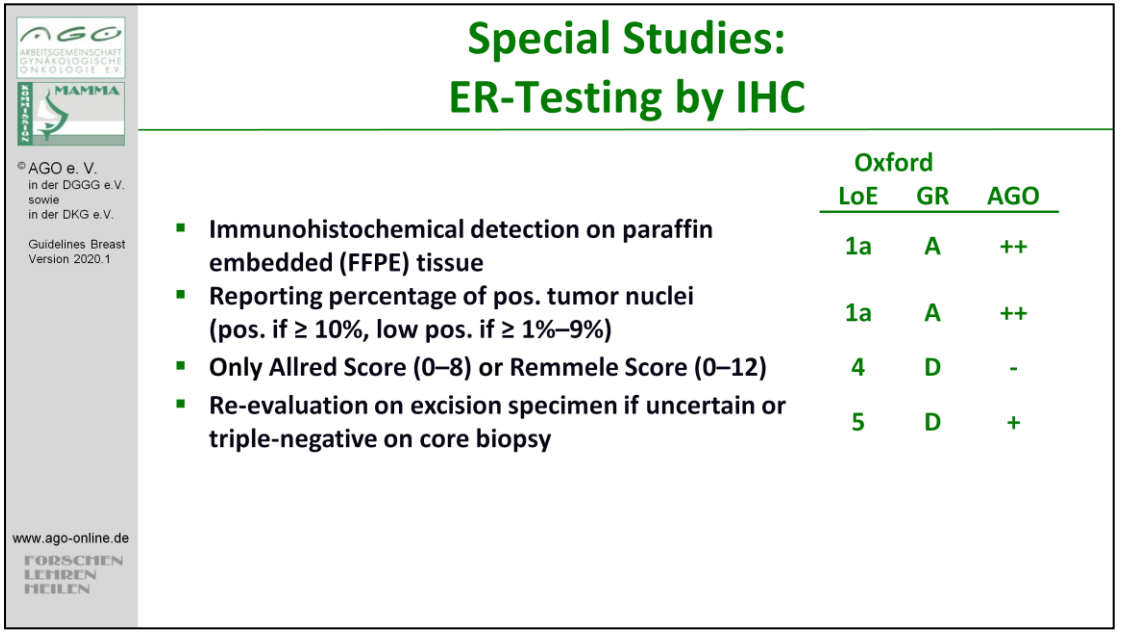

IHC-testing for ER-positivity

1. Allred, D. C. (2010). Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Modern Pathology, 23 Suppl 2, S52–9. doi:10.1038/modpathol.2010.55
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5. 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.

6. 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
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IHC Scores

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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

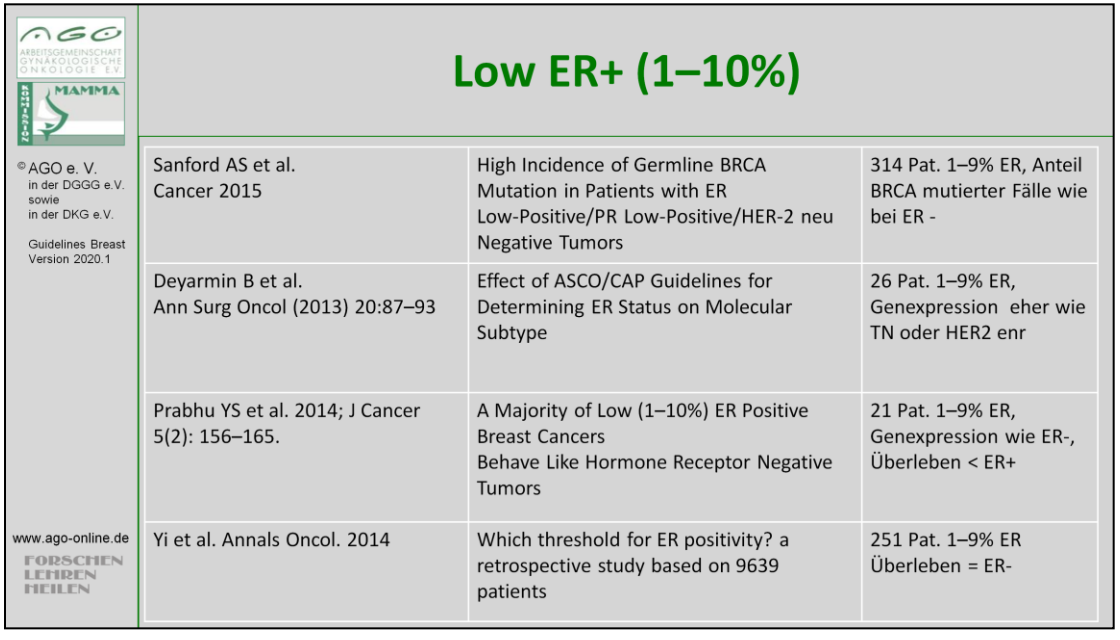
1. Cheang MC, Treaba DO, Speers CH, et al. Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival.J Clin Oncol. 2006 Dec 20;24(36):5637-44.

Low ER+ Group (≥1%<10%)

1. Gloyeske, N. C., Dabbs, D. J., & Bhargava, R. (2014). Low ER+ Breast Cancer: Is This a Distinct Group? American Journal of Clinical Pathology, 141(5), 697–701.
2. Iwamoto, T., Booser, D., Valero, V., et al. (2012). Estrogen Receptor (ER) mRNA and ER-Related Gene Expression in Breast Cancers That Are 1% to 10% ER-Positive by Immunohistochemistry. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 30(7), 729–734.
3. Sanford AS et al. High Incidence of Germline BRCA Mutation in Patients with ER Low-Positive/PR Low-Positive/HER-2 neu Negative

Tumors. Cancer 2015

4. Deyarmin B et al. Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype. Ann Surg Oncol (2013) 20:87–93
5. Yi et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. Annals Oncol. 2014



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. 1–9% 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. 1–9% 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-

IHC-testing for ER-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. 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
3. Gown, A. M. (2008). Current issues in ER and HER2 testing by IHC in breast cancer. *Modern Pathology*, *21*, S8–S15
4. Hammond, M. E. H., Hayes, D. F., Dowsett, M. et al. (2010, July). American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Archives of Pathology & Laboratory Medicine*. Arch Pathol Lab Med.
5. 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.

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.

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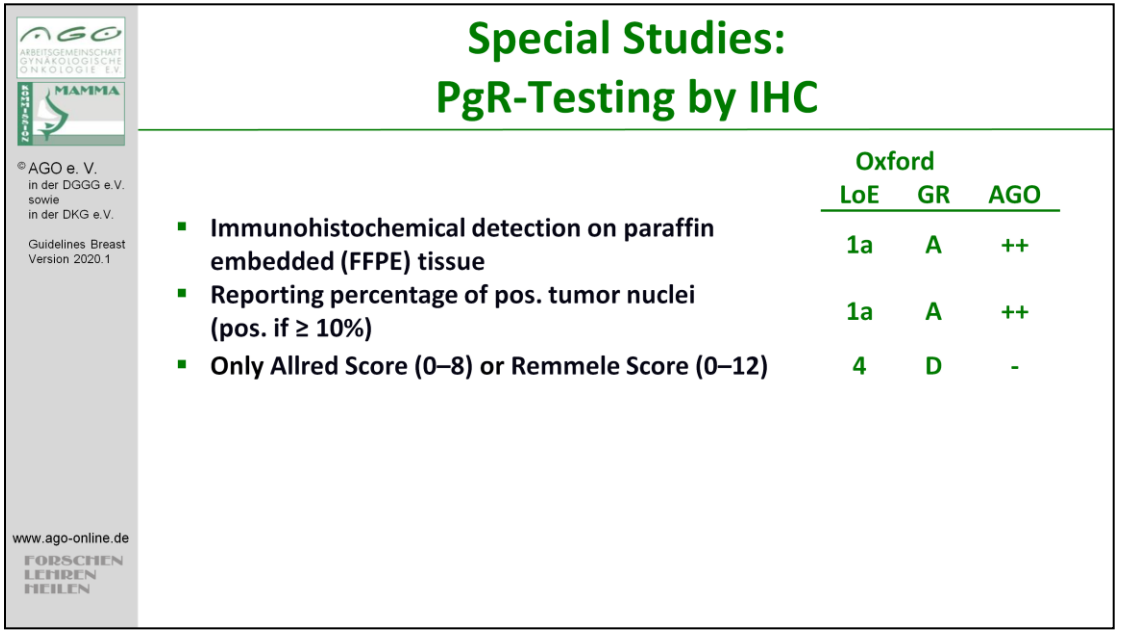
Low ER+ Group

1. Gloyeske, N. C., Dabbs, D. J., & Bhargava, R. (2014). Low ER+ Breast Cancer: Is This a Distinct Group? *American Journal of Clinical Pathology*, *141*(5), 697–701.
2. Iwamoto, T., Booser, D., Valero, V. et al. (2012). Estrogen Receptor (ER) mRNA and ER-Related Gene Expression in Breast Cancers That Are 1% to 10% ER-Positive by Immunohistochemistry. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *30*(7), 729–734.
3. 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
4. Deyarmin B et al. Ann Surg Oncol (2013) 20:87–93. Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype
5. 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.
6. Yi et al. Annals Oncol. 2014 Which threshold for ER positivity? a retrospective study based on 9639 patients



IHC-testing for PR-positivity

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

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

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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.

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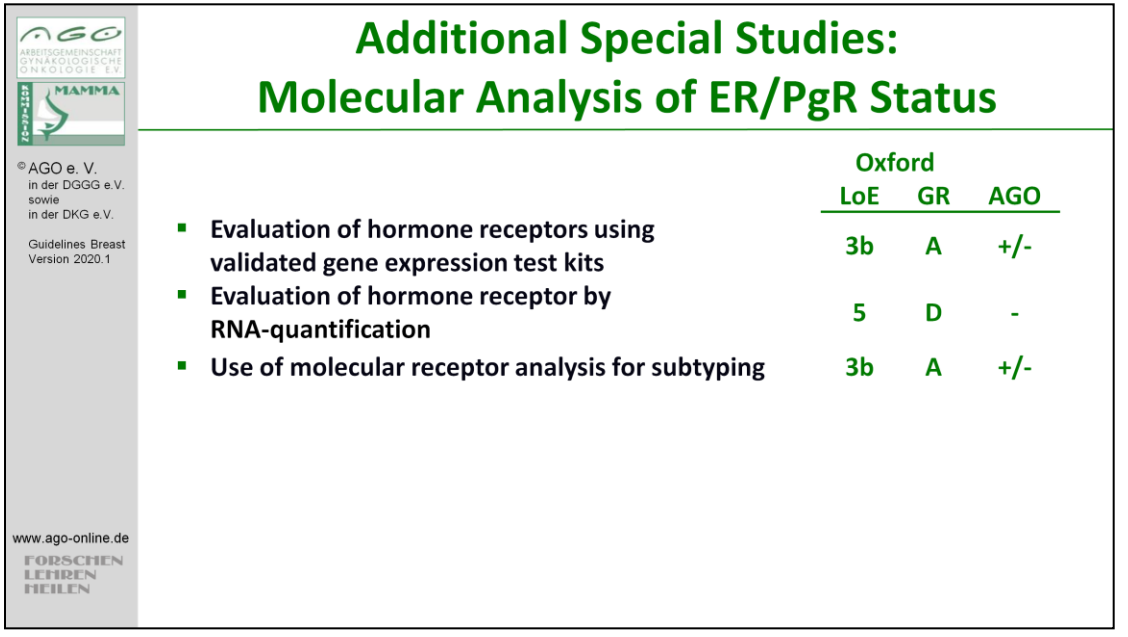
2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) fur den immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.



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

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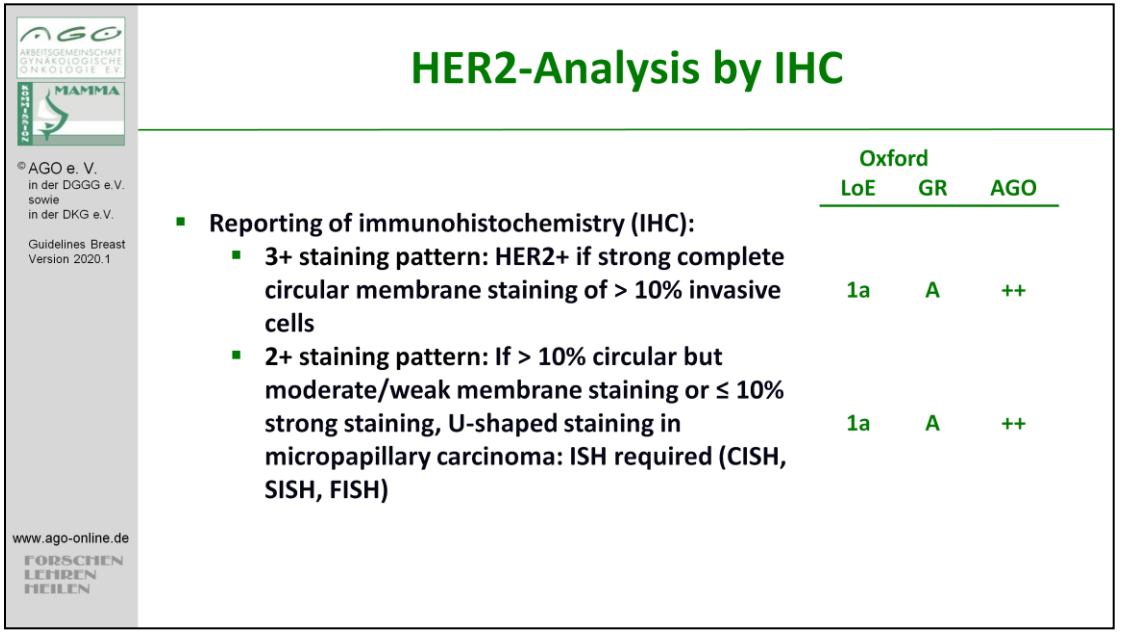

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2. Chivukula M, Bhargava R, Brufsky A et al. (2008) Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. Mod Pathol 21:363-368
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5. Taucher S, Rudas M, Mader Rm et al. (2004) Prognostic markers in breast cancer: the reliability of HER2/neu status in core needle biopsy of 325 patients with primary breast cancer. Wien Klin Wochenschr 116:26-31
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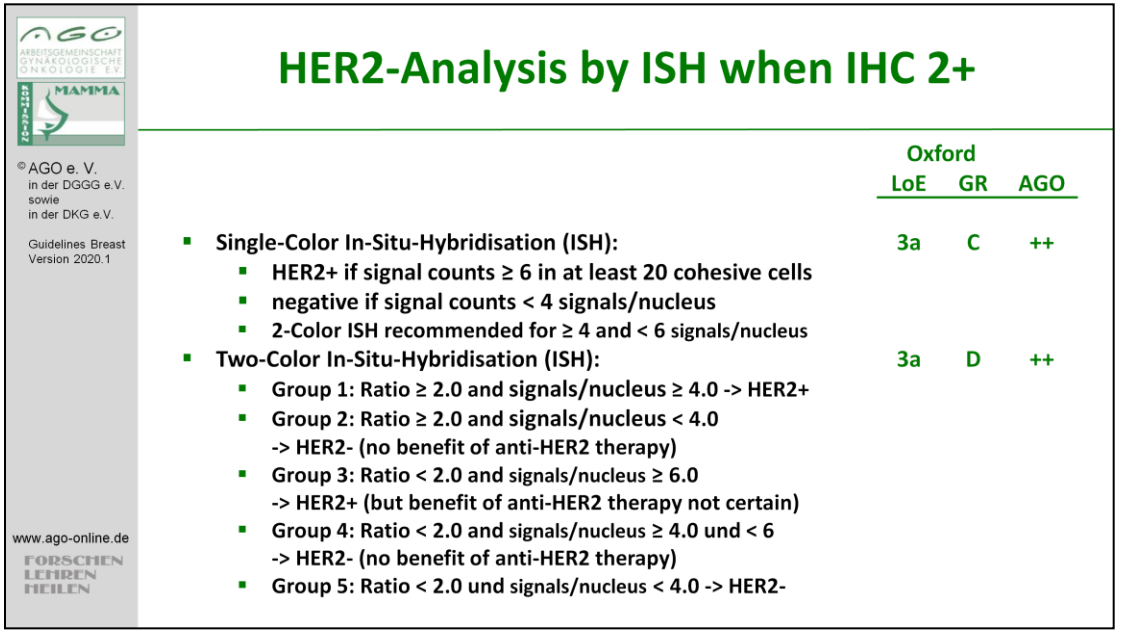
7. Wolff AC, Hammond ME, Hicks DG, et al. American Society of Clinical Oncology; College of American Pathologists.Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of

Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31:3997-4013

8. 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. 2017 Dec 22. doi: 10.1038/modpathol.2017.171



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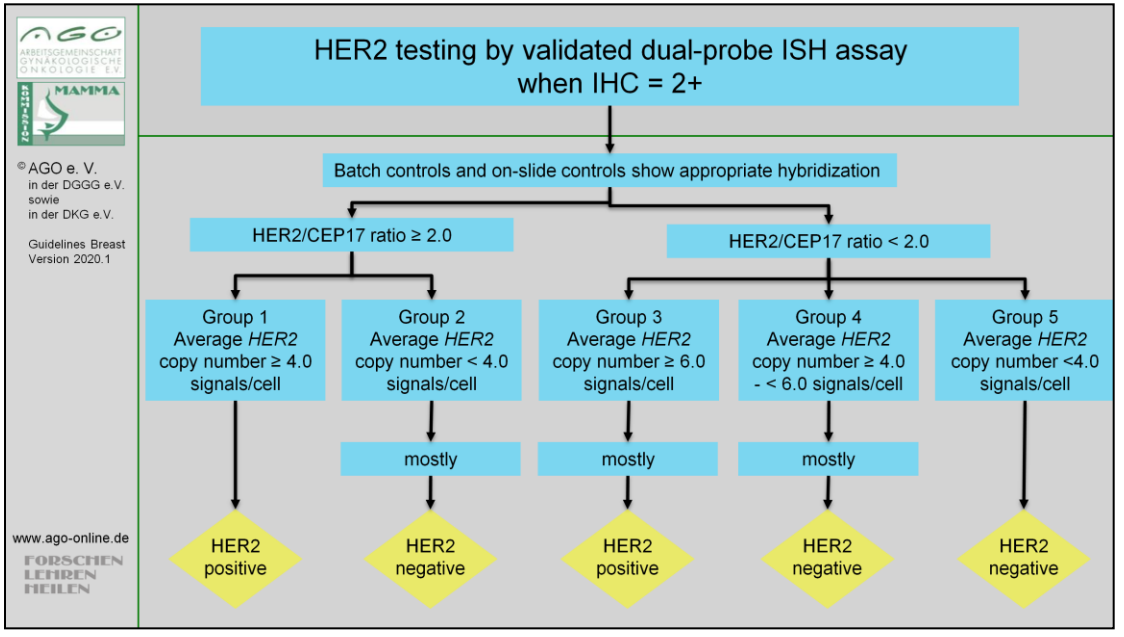
HER2 testing by validated dual-probe ISH assay when IHC = 2+
Batch controls and on-slide controls show appropriate hybridization
HER2/CEP17 ratio ≥ 2.0
HER2/CEP17 ratio < 2.0
Group 1 Average HER2 copy number ≥ 4.0 signals/cell
Group 2 Average HER2 copy number < 4.0 signals/cell
Group 3 Average HER2 copy number ≥ 6.0 signals/cell
Group 4 Average HER2 copy number ≥ 4.0 - < 6.0 signals/cell
Group 5 Average HER2 copy number <4.0 signals/cell
mostly
mostly
mostly
HER2 positive
HER2 negative
HER2 positive
HER2 negative
HER2 negative
© AGO e. V.
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Guidelines Breast
Version 2020.1
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FORSCHEN
LEHREN
HEILEN

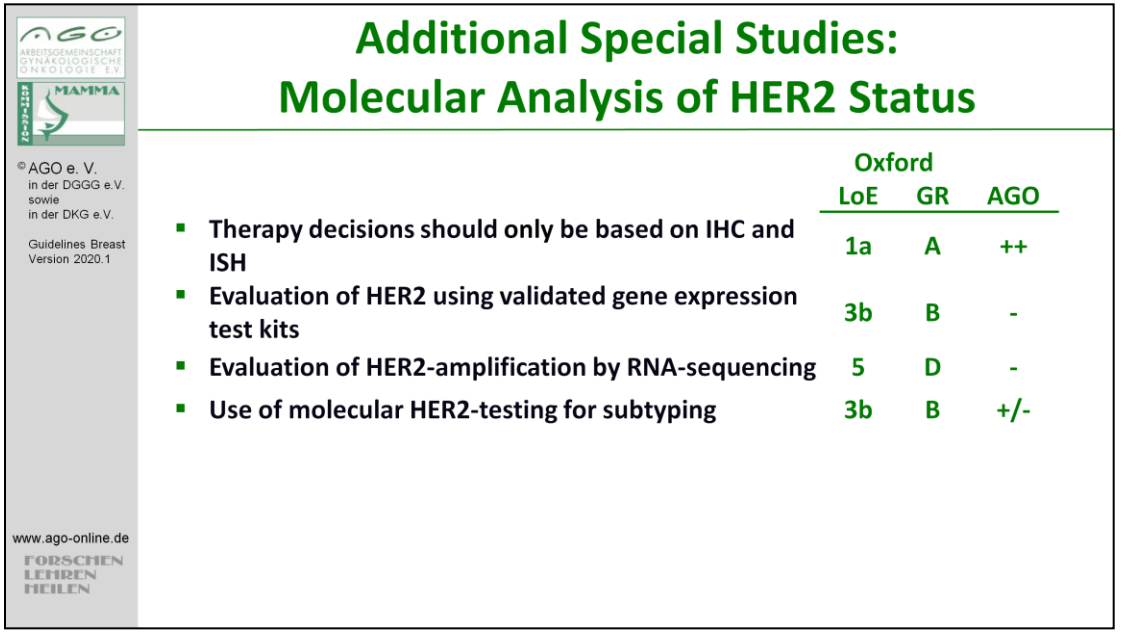
HER2 Testing on Core Biopsies

Guidelines Breast
Version 2020.1

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 PgR 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



Clinical significance of mRNA expression of HER2 and concordance with IHC results

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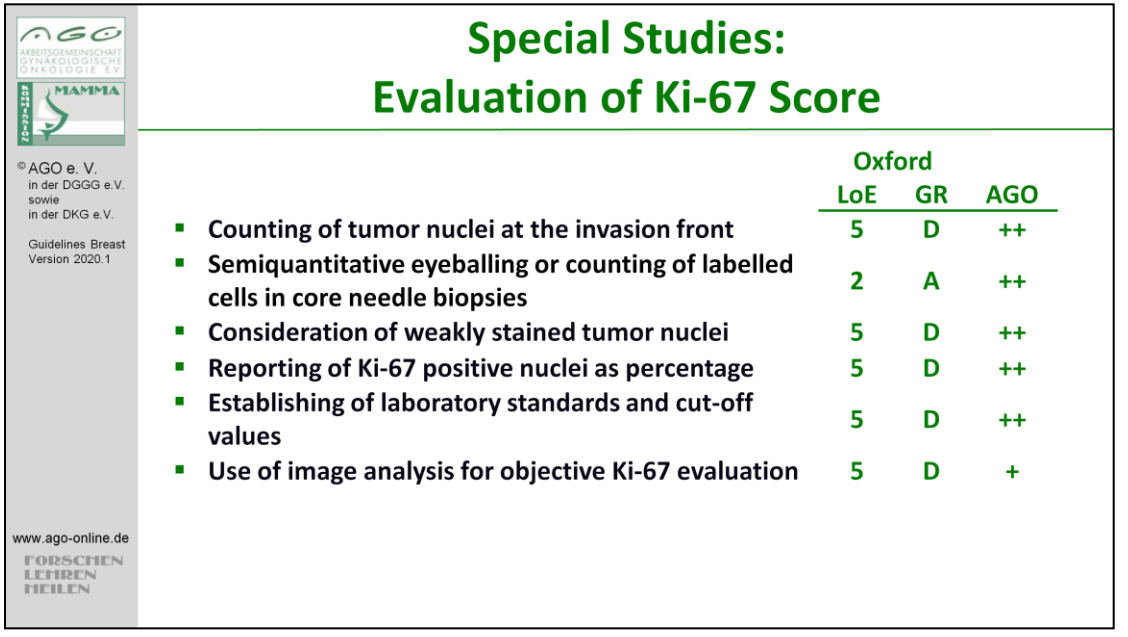

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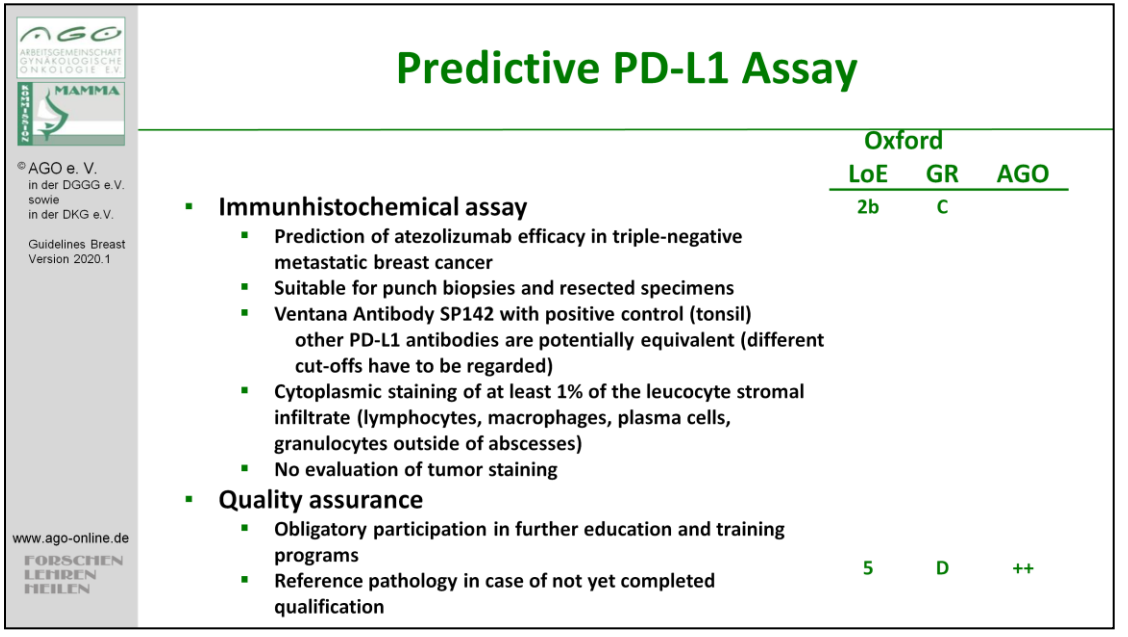

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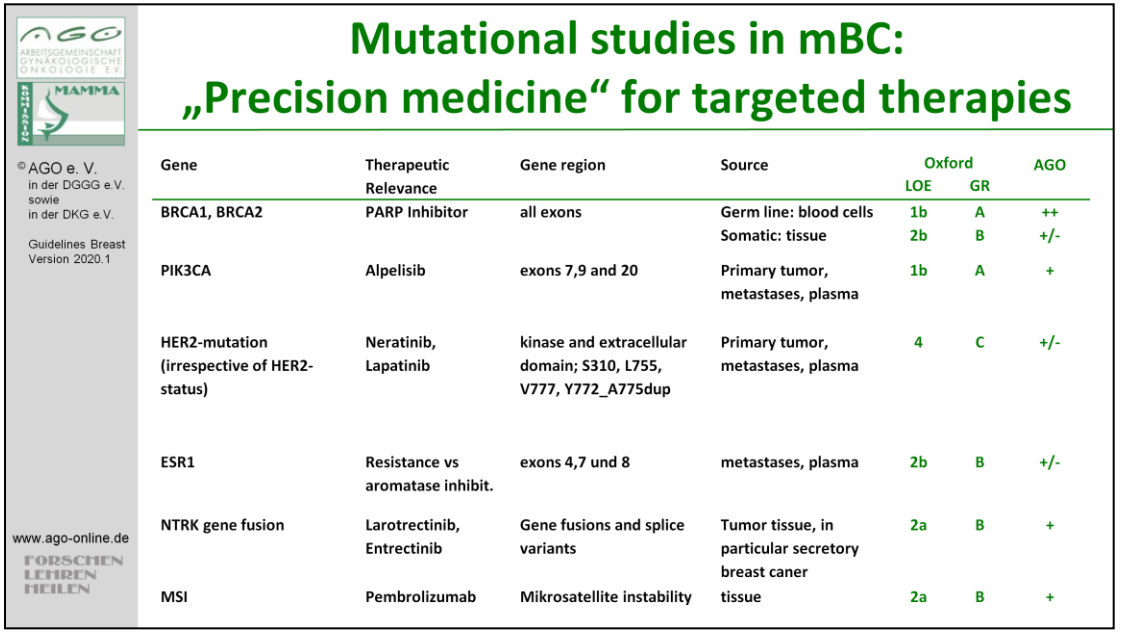

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FDA Zulassung entitätsübergreifend (23.5.17): Full prescribing information for pembrolizumab is available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf