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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Pathology



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# Pathology

- **Versions 2004–2018:**  
**Blohmer / Costa / Fehm / Friedrichs / Huober /  
Kreipe / Lück / Schneeweiss/ Sinn / Thomssen /  
Schmidt**
- **Version 2019:**  
**Sinn / Maass**

Screened data bases: PubMed 2018.

### 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](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\\_II\\_mammaca\\_11\\_02\\_2008.pdf](http://www.senologie.org/download/pdf/s3_II_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>
10. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8



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## Preanalytics: Fixation

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

### Antigen preservation


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

American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Archives of Pathology & Laboratory Medicine*, arpa.2018–0902–SA. <http://doi.org/10.5858/arpa.2018-0902-SA>

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

#### Retraction artifacts

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



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## Use of Breast Cytology\*

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

- Nipple secretion
- Tumor
- Cyst
- Lymph node

\* Ultrasound-guided core biopsy recommended

1. Day, C, N Moatamed, AM Fimbres, et al: A Retrospective Study of the Diagnostic Accuracy of Fine-Needle Aspiration for Breast Lesions and Implications for Future Use. *Diagnostic Cytopathology* 36, no. 12 (November 30, 2008): 855–60.
2. Pinder, S E, and J S Reis-Filho. Non-Operative Breast Pathology. *Journal of Clinical Pathology* 60, no. 12 (December 20, 2006): 1297–99. doi:10.1136/jcp.2006.040519.
3. Tse, G M K, T K F Ma, P C W Lui, et al. Fine Needle Aspiration Cytology of Papillary Lesions of the Breast: How Accurate Is the Diagnosis?. *Journal of Clinical Pathology* 61, no. 8 (August 2008): 945–49. doi:10.1136/jcp.2008.057489.
4. Ibrahim AE, Bateman AC, Theaker JM, et al. The role and histological classification of needle core biopsy in comparison with fine needle aspiration cytology in the preoperative assessment of impalpable breast lesions. *J Clin Pathol* 2001;54:121–5.
5. He, X., Wang, Y., Nam, G., 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>

Workup: Core Needle Biopsies (US-guided or stereotactic)			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Routine workup in step sections (14G: 1–3 step sections / 11G, 8G: 6–8 step sections)</li> </ul>	5	D	++
<ul style="list-style-type: none"> <li>Correlation with imaging (density, calcifications), use of B-classification</li> </ul>	1b	B	++
<ul style="list-style-type: none"> <li>Frozen section diagnosis on core biopsies</li> </ul>	5	D	--
<ul style="list-style-type: none"> <li>Routine evaluation of ER/PgR and HER2 status</li> </ul>	3b	C	++
<ul style="list-style-type: none"> <li>Turn-around time &lt; 24 h (histology)</li> </ul>	5	D	+

#### Statement: Routine workup in step sections

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

#### Statement: Correlation with imaging

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



Statement: Frozen section diagnosis on core biopsies

1. Lebeau, Gerber, Brucker et al. (2017): Pathomorphologische Untersuchung. In: AWMF: S3-Leitlinie Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, S. 100 - 139.
2. Dämmrich, M., Thomssen, C., Hillemanns, P. et al. (2012). Intraoperative pathologische Sofortuntersuchung in der Mammachirurgie. *Der Pathologe*, 33(5), 424–429. <http://doi.org/10.1007/s00292-012-1596-6>

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

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

Statement: Turn-around time < 24h

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

## Workup: Breast-Conserving Specimens


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

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.
3. Gage I, Schnitt SJ, Nixon AJ et al. Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. Cancer. 1996;78:1921-1928


## Workup: Mastectomy Specimens

	Oxford		
	LoE	GR	AGO
▪ <b>Margins always to be sampled</b>			
▪ Skin close to tumor	5	D	++
▪ Deep margin			
▪ Other margins, if close (< 1 cm)			
▪ <b>Attention to soft tissue margins in skin sparing mastectomy</b>	5	D	++
▪ <b>Routine sampling of uninvolved quadrants, skin above tumor, and retroareolar region</b>	5	D	++
▪ <b>Systematic sampling in prophylactic mastectomies (BRCA-1/2 pos. patients)</b>	5	D	++

1. 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: 1026-1033.
2. Association of Directors of Anatomic and Surgical Pathology. Recommendations for quality assurance and improvement in surgical and autopsy pathology. Hum Pathol (2006) vol. 37 (8) pp. 985-8
3. A. 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/>



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# Workup: Sentinel Node Biopsy

	Oxford		
	LoE	GR	AGO
▪ <b>Full workup using step sections of <math>\leq 500 \mu\text{m}</math> on paraffin embedded tissue</b>	5	D	++
▪ <b>Cytokeratin immunohistochemistry</b>			
▪ When suspicious, to detect micrometastases	2b	B	+
▪ For micrometastasis detection after NACT	2b	B	+
▪ As a routine procedure	5	D	+/-
▪ <b>Frozen section (compromises paraffin histomorphology)</b>			
▪ If clinical consequence	5	D	+/-
▪ If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BCT)	5	D	-
▪ <b>Imprint cytology instead of, or in addition to frozen section</b>	3b	D	+/-
▪ <b>RT-PCR for epithelial genes</b>	4	D	-
▪ OSNA	3b	B	-

### Statement: Evaluation of sentinel node biopsy

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

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

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

### Statement: Frozen section

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

Statement: Imprint cytology instead or in addition of frozen section

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

Statement: RT-PCR for epithelial genes

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

Workup: Intraoperative pathologic evaluation and frozen sections			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li> <b>Sentinel node biopsy for invasive cancer (compromises final paraffin histomorphology)</b> <ul style="list-style-type: none"> <li>If clinical consequence</li> <li>No clinical consequence</li> </ul> </li> <li> <b>Closest margin of resection</b> <ul style="list-style-type: none"> <li>If macroscopically &lt; 1 cm</li> <li>If macroscopically &gt; 1 cm</li> </ul> </li> <li> <b>Lesions ≥ 1 cm, without core biopsy</b> </li> <li> <b>Non-palpable lesions or lesions &lt; 1 cm</b> </li> <li> <b>Conservation of fresh tissue (tumor banking)</b> </li> </ul>	 5 5  5 5 5 5 5	 D D  D D D D D	 + -  + - + -- +

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#### 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, Torrenge H, Borgstein PJ et al. Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. Histopathology 1999; 35: 14-18.

#### Statement: Closest margin of resection


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

Statement: Lesions  $\geq$  1 cm, without core biopsy

1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthal R, Helfer L, Hrsg.). <http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/>
2. Fitzgibbons PL, Connolly JL, Page DL. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Arch Pathol Lab Med 2000; 124:1026- 1033. (ACR)
3. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, et al (eds) European guidelines for quality assurance in breast cancer screening and diagnosis; Office for Official Publications of the European Communities, Luxembourg, 2006, pp 256-311

Statement: Non-palpable lesions or lesions  $<$  1 cm

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



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## Reporting: Histologic Tumor Type


- **Histologic tumor typing according to WHO-Classification, (4th ed., 2012)**
  - **Partial special differentiation:**  
> 50% NST component  
and < 50% special tumor type (minor component)
  - **Mixed differentiation:**  
> 50% special tumor type  
and < 50% NST component  
Example: mucinous breast cancer, mixed type
  - **Pure types:**  
> 90% special tumor type  
Examples: tubular or cribriform Ca.

Oxford		
LoE	GR	AGO
3a	C	++

### 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-myoeptithelial, 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





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## Reporting: Grade of Malignancy


	Oxford LoE	GR	AGO
■ Use of Nottingham grading system (Elston & Ellis 1991) for all types of invasive breast cancer	5	D	++
■ In case of very little tumor tissue, pure nuclear grading or additional criteria, such as Ki-67 proliferation fraction, may be used	5	D	++
■ Grading of DCIS, e.g. according to WHO-Classification, (4th ed., 2012)	5	D	++
■ Reporting of tumor grading in numeric form (e.g. G3)	5	D	++

### 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.



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## Reporting: Tumor Size and Total Extent of Tumor

	Oxford LoE	GR	AGO
▪ <b>Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results</b>	5	D	++
▪ <b>Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality</b>	5	D	++
▪ <b>Reporting of size of noninvasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2x invasive Ca)</b>	5	D	++

### Determination of tumor size

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


### Multifocality

1. Hilton, J. F., Bouganim, N., Dong, B., et al. (2013). Do alternative methods of measuring tumor size, including consideration of multicentric/multifocal disease, enhance prognostic information beyond TNM staging in women with early stage breast cancer: an analysis of the NCIC CTG MA.5 and MA.12 clinical trials. Breast Cancer Research and Treatment, 142(1), 143–151.
2. NHS (2005) Pathology Reporting of Breast Disease. IA Joint Document Incorporating the Third Edition of the NHS Breast Screening Programme's Guidelines for Pathology Reporting in Breast Cancer Screening and the Second Edition of The Royal College of Pathologists' Minimum Dataset for Breast Cancer Histopathology  
<http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58-low-resolution.pdf>

3. Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. *Annals of Oncology*. 2008 Apr 1;19(4):614–22.
4. Tot, T., Gere, M., Pekár, G., et al. (2011). Breast cancer multifocality, disease extent, and survival. *Human Pathology*, 42(11), 1761–1769.

#### Extensive intraductal component (EIC)

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



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## Reporting: pTNM

Oxford		
LoE	GR	AGO
5	D	++

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

### 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: Involvement of the skin

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

### pT4d category: Inflammatory breast cancer

1. Yamauchi, H., Woodward, W. A., Valero, V., et al. (2012). Inflammatory breast cancer: what we know and what we need to learn.

The Oncologist, 17(7), 891–899. doi:10.1634/theoncologist.2012-0039

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



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### 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.
5. 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
6. 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

7. 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

#### R-Classifikation

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



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## Reporting: Lymphovascular Invasion

	Oxford LoE	GR	AGO
▪ <b>L1: Lymphovascular invasion</b>			
<b>L0: No lymphovascular invasion</b>	5	D	++
▪ <b>IHC for evaluation of lymphovascular invasion</b>	3b	C	-
▪ <b>Differentiation of peritumoral and extensive lymphovascular invasion</b>	3b	C	++
▪ <b>Reporting of venous invasion (V0/V1) optional, prognostic significance not established</b>	5	D	+

### Definition of L- and V-Classification

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


### Detection of angioinvasion

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



#### Prognostic significance of lymphovascular invasion

1. Gujam, F. J. A., Going, J. J., Edwards, J. et al. (2014). The role of lymphatic and blood vessel invasion in predicting survival and methods of detection in patients with primary operable breast cancer. *Critical Reviews in Oncology/Hematology*, 89(2), 231–241. doi:10.1016/j.critrevonc.2013.08.014
2. Colleoni, M., Rotmensz, N., Maisonneuve, P., et al. (2007). Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. *Annals of Oncology*, 18(10), 1632–1640
3. Rakha, E. A., Martin, S., Lee, A. H. S., et al. (2011). The prognostic significance of lymphovascular invasion in invasive breast carcinoma. *Cancer*, 118(15), 3670–3680.



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## Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)


Oxford		
LoE	GR	AGO
5	D	+/-

- **Identification of tumors with predominant lymphocytic infiltrate (> 50%) in tumor stroma (according to Salgado et al.\*)**  
**Consider only lymphocytic infiltrate in tumor stroma and not at the invasion front**  
**Do not consider central fibrosis and necrotic areas**  
**Report average of lymphocytic infiltrate as percentage**

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

### Definition and impact of predominant lymphocytic infiltration

1. Salgado, R., Denkert, C., Demaria, S., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Annals of Oncology*.
2. Denkert, C., Minckwitz, von, G., Brase, J. C., et al. (2014). Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, JCO.2014.58.1967. doi:10.1200/JCO.2014.58.1967
3. Denkert C, Wienert S, Poterie A, et al. Standardized evaluation of tumor-infiltrating lymphocytes in breast cancer: results of the ring studies of the international immuno-oncology biomarker working group. *Mod Pathol*. 2016 Oct;29(10):1155-64
4. Loi, S., Sirtaine, N., Piette, F et al. (2013). Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, 31(7), 860–867.


	Oxford		
	LoE	GR	AGO
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▪ Identification of tumor bed, otherwise ypTX	4	D	++
▪ Reporting of tumor size as total extent of tumor bed area involved by infiltrates of residual vital invasive carcinoma	4	D	++
▪ pCR when absence of invasive Ca. and absence of angioinvasion or LN metastases. Presence of ypTis should be recorded	2b	D	+
▪ Use of IHC to identify tumor residues	4	D	+/-
▪ Reporting of ypTN after therapy	5	D	++
▪ Repeat IHC for ER, PgR, and HER2	5	D	+/-

### Specimen processing after neoadjuvant chemotherapy

1. Sahoo, S., & Lester, S. C. (2009). Pathology of breast carcinomas after neoadjuvant chemotherapy: an overview with recommendations on specimen processing and reporting. Archives of Pathology & Laboratory Medicine, 133(4), 633–642.

### RCB-Score

1. RCB-Calculator: <http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3>
2. 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.
3. Sheri, A., Smith, I. E., Johnston, S. R. et al. (2015). Residual proliferative cancer burden to predict long-term outcome following neoadjuvant chemotherapy. Annals of Oncology, 26(1), 75–80.



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## Special Studies: ER-Testing by IHC

	Oxford LoE	GR	AGO
■ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
■ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%, low pos. if ≥ 1%–9%)	1a	A	++
■ Only Allred Score (0–8) or Remmele Score (0–12)	4	D	-
■ Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy	5	D	+

### 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](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., 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.
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
7. 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) für den immunhistochemischen Östrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

### Monoclonal Antibodies for ER-Testing


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

### Low ER+ Group ( $\geq 1\% < 10\%$ )

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



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## Special Studies: PgR-Testing by IHC

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

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

### IHC-testing for PR-positivity

1. Allred, D. C. (2010). Issues and updates: evaluating estrogen receptor-alpha, progesterone receptor, and HER2 in breast cancer. Modern Pathology, 23 Suppl 2, S52–9. doi:10.1038/modpathol.2010.55
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](http://www.nccn.org/JNCCN/PDF/2009_estrogen_receptor_and_progesterone_receptor_immunohistochemistry.pdf)
3. 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.
4. 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.

### 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) für den immunhistochemischen Östrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.



	<h2 style="text-align: center;">Low ER+ (1–10%)</h2>		
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	<p>Deyarmin B et al. Ann Surg Oncol (2013) 20:87–93</p>	<p>Effect of ASCO/CAP Guidelines for Determining ER Status on Molecular Subtype</p>	<p>26 Pat. 1–9% ER, Genexpression eher wie TN oder HER2 enr</p>
	<p>Prabhu YS et al. 2014; J Cancer 5(2): 156–165.</p>	<p>A Majority of Low (1–10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors</p>	<p>21 Pat. 1–9% ER, Genexpression wie ER-, Überleben &lt; ER+</p>
	<p>Yi et al. Annals Oncol. 2014</p>	<p>Which threshold for ER positivity? a retrospective study based on 9639 patients</p>	<p>251 Pat. 1–9% ER Überleben = ER-</p>

### 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](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) für den immunhistochemischen Östrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. *Der Pathologe*, 8(3), 138–140.

### Monoclonal Antibodies for ER-Testing

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

### 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



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## Additional Special Studies: Molecular Analysis of ER/PgR Status

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

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

1. Denkert, C., Huober, J., Loibl, S., et al. (2013). HER2 and ESR1 mRNA expression levels and response to neoadjuvant trastuzumab plus chemotherapy in patients with primary breast cancer. Breast Cancer Research : BCR, 15(1), R11. doi:10.1186/bcr3384
2. Kim, C., Tang, G., Pogue-Geile, K. L., et al. (2011). Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(31), 4160–4167. doi:10.1200/JCO.2010.32.9615
3. Nguyen, B., Cusumano, P. G., Deck, K., et al. (2012). Comparison of molecular subtyping with BluePrint, MammaPrint, and TargetPrint to local clinical subtyping in breast cancer patients. Annals of Surgical Oncology, 19(10), 3257–3263. doi:10.1245/s10434-012-2561-6
4. Pentheroudakis, G., Kalogeras, K. T., Wirtz, R. M., et al. (2009). Gene expression of estrogen receptor, progesterone receptor and microtubule-associated protein Tau in high-risk early breast cancer: a quest for molecular predictors of treatment benefit in the context of a Hellenic Cooperative Oncology Group trial. Breast Cancer Research and Treatment, 116(1), 131–143.
5. Viale, G., Slaets, L., Bogaerts, J., et al. (2014). 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. Annals of Oncology, 25(4),

816–823.

6. Robinson DR, Wu YM, Vats P et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. *Nat Genet* 2013;45:1446-1451. doi: 10.1038/ng.2823
7. Schiavon G, Hrebien S, Garcia-Murillas I et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. *Sci Transl Med* 2015;7:313ra182. doi: 10.1126/scitranslmed.aac7551.
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## HER2-Analysis by IHC

### ■ Reporting of immunohistochemistry (IHC):

- **3+ staining pattern: HER2+ if strong complete circular membrane staining of > 10% invasive cells**
- **2+ staining pattern: If > 10% circular but moderate/weak membrane staining or ≤ 10% strong staining, U-shaped staining in micropapillary carcinoma: ISH required (CISH, SISH, FISH)**


Oxford		
LoE	GR	AGO
1a	A	++

1a	A	++
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## HER2-Analysis by ISH when IHC 2+

	Oxford	LoE	GR	AGO
<ul style="list-style-type: none"> <li>▪ <b>Single-Color In-Situ-Hybridisation (ISH):</b> <ul style="list-style-type: none"> <li>▪ HER2+ if signal counts <math>\geq 6</math> in at least 20 cohesive cells</li> <li>▪ negative if signal counts <math>&lt; 4</math> signals/nucleus</li> <li>▪ 2-Color ISH recommended for <math>\geq 4</math> and <math>&lt; 6</math> signals/nucleus</li> </ul> </li> <li>▪ <b>Two-Color In-Situ-Hybridisation (ISH):</b> <ul style="list-style-type: none"> <li>▪ Group 1: Ratio <math>\geq 2.0</math> and signals/nucleus <math>\geq 4.0</math> -&gt; HER2+</li> <li>▪ Group 2: Ratio <math>\geq 2.0</math> and signals/nucleus <math>&lt; 4.0</math> -&gt; HER2- (no benefit of anti-HER2 therapy)</li> <li>▪ Group 3: Ratio <math>&lt; 2.0</math> and signals/nucleus <math>\geq 6.0</math> -&gt; HER2+ (but benefit of anti-HER2 therapy not certain)</li> <li>▪ Group 4: Ratio <math>&lt; 2.0</math> and signals/nucleus <math>\geq 4.0</math> und <math>&lt; 6</math> -&gt; HER2- (no benefit of anti-HER2 therapy)</li> <li>▪ Group 5: Ratio <math>&lt; 2.0</math> und signals/nucleus <math>&lt; 4.0</math> -&gt; HER2-</li> </ul> </li> </ul>	3a	C	++	
	3a	D	++	

1. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-1672.
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3. Romond EP, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-1684.
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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  $\geq 2.0$

HER2/CEP17 ratio  $< 2.0$

Group 1  
Average HER2  
copy number  $\geq 4.0$   
signals/cell

Group 2  
Average HER2  
copy number  $< 4.0$   
signals/cell

Group 3  
Average HER2  
copy number  $\geq 6.0$   
signals/cell

Group 4  
Average HER2  
copy number  $\geq 4.0$   
-  $< 6.0$  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

## HER2 Testing on Core Biopsies


**False positive immunohistochemical labeling may occur in core biopsies.**

**Therefore, methods of individual laboratories should be validated by comparison of core biopsies and resection specimens. Background staining should be evaluated by comparison with normal duct epithelium.**

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

**False positivity is likely when HER+ was reported in G1 tumors of the following types: Infiltrating ductal or lobular carcinoma, ER and 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**



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## Additional Special Studies: Molecular Analysis of HER2 Status

	Oxford LoE	GR	AGO
■ <b>Therapy decisions should be based on IHC and ISH only</b>	1a	A	++
■ <b>Evaluation of HER2 using validated gene expression test kits</b>	3b	B	-
■ <b>Evaluation of HER2-amplification by RNA-sequencing</b>	5	D	-
■ <b>Use of molecular HER2-testing for subtyping</b>	3b	B	+/-

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

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Special Studies: Evaluation of Ki-67 Score			
	Oxford		
	LoE	GR	AGO
■ Counting of tumor nuclei at the invasion front	5	D	++
■ Semiquantitative eyeballing or counting of labelled cells in core needle biopsies	2	A	++
■ Consideration of weakly stained tumor nuclei	5	D	++
■ Reporting of Ki-67 positive nuclei as percentage	5	D	++
■ Establishing of laboratory standards and cut-off values	5	D	++
■ Use of image analysis for objective Ki-67 evaluation	5	D	+



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### Ki-67 Methods and Reproducibility

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#### Impact of Ki-67 staining

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#### Ki-67 Image Analysis

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## Intrinsic Breast Cancer Types (Molecular and Immunohistochemical Definitions)

- Currently there are no generally accepted and proven translation of molecularly defined types (basal, luminal A/B-Typ, HER2) into immunohistochemical counterparts neither with regard to markers nor to thresholds
- In terms of practical consequences, re-labeling of clinically established and immunohistochemically defined subgroups might be useful (ER/PR+ for luminal, HER2+ for HER2-type, triple negative for basal type)
- The basal type shows an 80% overlap with the triple negative subgroup of ductal invasive breast cancer (ER < 1% & PgR < 1% & HER2 0/1+2+ (non-amplified, ratio < 2))
- None of the available markers (Ki-67, grading, recurrence score etc.) can reliably discriminate between luminal A and luminal B type
- Although derived from RNA expression studies, RNA measurements are not suited for the definition of intrinsic types for purposes of therapy





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## Prädixtive PD-L1 Assay

	Oxford		
	LoE	GR	AGO
	2b	C	
<ul style="list-style-type: none"> <li>▪ <b>Immunhistochemical assay</b> <ul style="list-style-type: none"> <li>▪ Prediction of atezolizumab efficacy in triple-negative metastatic breast cancer</li> <li>▪ Suitable for punch biopsies and resected specimens</li> <li>▪ Ventana Antibody SP142 with Positive Control (tonsil)</li> <li>▪ Cytoplasmic staining of at least 1% of the leucocyte stromal infiltrate (lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses)</li> <li>▪ No evaluation of tumor staining</li> </ul> </li> <li>▪ <b>Quality assurance</b> <ul style="list-style-type: none"> <li>▪ Obligate participation in further education and training measures</li> <li>▪ Reference pathology in case of not yet completed qualification</li> </ul> </li> </ul>	5	D	++

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## Quality Assurance: Immunohistochemistry

- Use of automated staining platform
- Participation in ring trials
- Strict adherence and monitoring of requirements of preanalytics (fixation)
- Use of on-slide controls
- Plausibility controls (e.g. tumor type, grading)

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## Quality Assurance: HER2-Status

- Continuous documentation of HER2 tests
- Quality goal: Rate of HER2-positivity: 15%
- Use of standardised and validated HER2 test kits
- Participation in ring trials



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## Quality Assurance: Reporting

- **Responsibility of one or two pathologists with special expertise in breast pathology**
- **Regular interdisciplinary conferences with radiologic-pathologic correlation**
- **Participation in quality circles**