

Diagnostik und Therapie primärer und metastasierter Mammakarzinome

Pathologie

Pathologie

- **Versionen 2004–2017:**
Blohmer / Costa / Fehm / Friedrichs / Huober / Kreipe / Lück /
Schneeweiss/ Sinn / Thomssen
- **Version 2018:**
Kreipe / Schmidt

Screened data bases: PubMed 1970 – 2014

Guidelines screened

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2017
 - NCCN Breast cancer V.1.2014Cochrane: 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 Mammopathologie.
 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_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

Allgemeine Prinzipien der histopathologischen Untersuchung beim Mammakarzinom

- Jede Aussage in der histologischen Diagnose steht unter der Prämisse der klinischen Relevanz
- Die angewandte Nomenklatur richtet sich nach aktuellen Leitlinien und internationalen Klassifikationen
- Qualitätssichernde Maßnahmen sind in allen Bereichen der pathologischen Diagnostik erforderlich

1. The EBCC council: Breast cancer pathology - a manifesto for optimal care. 9th European Breast Cancer Conference (EBCC-9) March 19-21, 2014 <http://www.ecco-org.eu/Events/Past-conferences/EBCC9/Manifesto>
2. 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
3. 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
4. Liessem S, Winkens W, Jonigk D, et al. [Determination of tumor biological parameters in breast cancer: round robin testing for quality assurance]. Pathologe. 2014 Feb;35(1):61-71. doi: 10.1007/s00292-013-1837-3. Review. German.

Präanalyse: Fixation

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

Antigen preservation

1. Apple, S., Pucci, R., Lowe, A. C., et al. (2011). The effect of delay in fixation, different fixatives, and duration of fixation in estrogen and progesterone receptor results in breast carcinoma. American Journal of Clinical Pathology, 135(4), 592–598.
2. 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.
3. 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
4. Gown, A. M. (2008). Current issues in ER and HER2 testing by IHC in breast cancer. Modern Pathology, 21, S8–S15
5. 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
6. Wolff, A. C., Hammond, M. E. H., Hicks, D. G., et al. (2013, November 1). 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. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. American Society of Clinical Oncology.

Retraction artifacts

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

Indikationen der Feinnadel-Aspirations-Zytologie*

- Mamillensekret
- Tumor*
- Zyste
- Lymphknoten

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

* Ultraschall gesteuerte Stanzbiopsie empfohlen

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.

Aufarbeitung: Makroskopie und Präparateradiographie

- Berücksichtigung der präoperativen Befunde (z.B. multiple Herde, intraduktale Komponente, Bezug zu Nachbarstrukturen) bei der Makrodokumentation
- Routinemäßige Dokumentation klinisch relevanter Befunde durch Skizze oder Foto, unter Berücksichtigung der Topographie
- Präparateradiographie bzw. Scheibenradiographie bei nicht palpablen Läsionen und Mikroverkalkungen

Clinical-pathological correlation diagnostics

1. 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>

Image documentation

1. 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.
2. Reiner, A. (2004). ÖGP Qualitätstandards in der Pathologie, Version 6.7.2001, S. 3.8.3, <http://www.pathology.at/pathologinnen/qualitaetssicherung/86-qs-links>

Specimen radiography

1. Carlson, J. W., Birdwell, R. L., Gombos, E. C., et al. (2007). MRI-directed, wire-localized breast excisions: incidence of malignancy and recommendations for pathologic evaluation. Human Pathology, 38(12), 1754–1759.
2. Lester, S. C., Bose, S., Chen, Y.-Yet al. (2009). Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med,

133(10), 1515–1538.

3. Lester SC, Bose S, Chen Y-Y, Connolly JL, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ of the breast. *Arch Pathol Lab Med*. 2009 Jan;133(1):15–25.
4. 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.
5. Rubio IT, Mirza N, Sahin AA, et al. Role of specimen radiography in patients treated with skin-sparing mastectomy for ductal carcinoma in situ of the breast. *Ann Surg Oncol*. 2000 Aug;7(7):544–8.

Aufarbeitung: Stanzbiopsien (Ultraschall gesteuert / stereotaktisch)

- **Aufarbeitung in Schnittstufen**
(14G: min. 3 Stufen / 11G, 8G: 6-8 Stufen)
- **Radiologisch-pathologische Korrelation**
(Mikrokalk / Dichte), Anwendung der
B-Klassifikation
- **Schnellschnittdiagnostik an Stanzbiopsien**
- **Evaluation des ER/PgR und HER2-Status**
- **Umlaufzeit < 24 h (Dignität)**

Oxford		
LoE	GR	AGO
5	D	++
1b	B	++
5	D	--
3b	C	++
5	D	+

Statement: Routine workup in step sections

1. Krainick-Strobel U, Hahn M, Duda VF, et al. Consensus recommendations for the application and indication of the vacuum biopsy of the breast under ultrasound view. Geburtshilfe Und Frauenheilkunde 65: 526-9, 2005
2. 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

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

Statement: Frozen section diagnosis on core biopsies

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

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

1. Harris G, Denley H, Pinder S et al. Correlation of histologic prognostic factors in core biopsies and therapeutic excisions of invasive breast carcinoma. Am J Surg Pathol 2003; 27: 11-15.
2. Chivukula M, Bhargava R, Brufsky A et al. Clinical importance of HER2 immunohistologic heterogeneous expression in core-needle biopsies vs resection specimens for equivocal (immunohistochemical score 2+) cases. Mod Pathol 2008; 21: 363-368.
3. Wood B, Junckerstorff R, Sterrett G et al. A comparison of immunohistochemical staining for oestrogen receptor, progesterone receptor and HER-2 in breast core biopsies and subsequent excisions. Pathology 2007; 39: 391-395.

Statement: Turn-around time < 24h

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

Aufarbeitung: Brusterhaltende Therapie

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

1. Sinn HP, Anton HW, Magener A, von Fournier D, Bastert G, Otto HF.
2. 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.
3. 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.
4. 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

Aufarbeitung: Mastektomie

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

Aufarbeitung: Sentinel-Lymphknoten

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

Statement: Evaluation of sentinel node biopsy

1. Kühn T, Bembenek A, Decker T et al. (2005) A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer 103:451-461

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

1. Kühn T, Bembenek A, Decker T et al. (2005) A concept for the clinical implementation of sentinel lymph node biopsy in patients with breast carcinoma with special regard to quality assurance. Cancer 103:451-461
2. Cserni G. (2004) Surgical pathological staging of breast cancer by sentinel lymph node biopsy with special emphasis on the histological work-up of axillary sentinel lymph nodes. Breast Cancer. 11: 242-9

Statement: Frozen section

1. Grabau DA, Rank F, Friis E (2005). Intraoperative frozen section examination of axillary sentinel lymph nodes in breast cancer. APMIS. 113:7-12

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. Limberis V, Romanidis C, Galazios G, et al. Intraoperative estimation of sentinel lymph nodes in breast cancer by imprint cytology. *European journal of gynaecological oncology*. 2009;30(1):85-7.

Statement: RT-PCR for epithelial genes

1. Brown, NM, TT Stenzel, PN Friedman, et al. "Evaluation of Expression Based Markers for the Detection of Breast Cancer Cells.." *Breast Cancer Research : BCR* 97, no. 1 (April 30, 2006): 41–47.
2. Snook, K L, G T Layer, P A Jackson, et al. "Multicentre Evaluation of Intraoperative Molecular Analysis of Sentinel Lymph Nodes in Breast Carcinoma." *The British Journal of Surgery*, December 23, 2010.

Aufarbeitung: Intraoperative pathologische Sofortuntersuchung einschließlich Schnellschnitt

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Sentinelbiopsie beim invasiven Karzinom (anschließender Paraffinschnitt erschwert) <ul style="list-style-type: none"> ■ bei klinischer Konsequenz ■ bei nicht zu erwartender Konsequenz 	5 5	D D	+ -
<ul style="list-style-type: none"> ■ Beurteilung der Resektionsränder <ul style="list-style-type: none"> ■ wenn makroskopisch < 1 cm ■ wenn makroskopisch > 1 cm 	5 5	D D	+ -
<ul style="list-style-type: none"> ■ Läsion mit einer Größe von ≥ 1 cm, keine Corebiopsie erfolgt 	5	D	+
<ul style="list-style-type: none"> ■ Nicht tastbare Läsion oder Läsion < 1 cm 	5	D	--
<ul style="list-style-type: none"> ■ Asservierung von unfixiertem Nativgewebe 	5	D	+

Statement: Sentinel node biopsy for invasive cancer

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

Statement: Closest margin of resection

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

Statement: Lesions ≥ 1 cm, without core biopsy

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

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

Statement: Non-palpable lesions or lesions < 1 cm

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

Befundung: Histologischer Tumortyp

Oxford		
LoE	GR	AGO
3b	C	++

- **Histologischer Tumortyp entsprechend WHO-Klassifikation (4. Aufl. 2012)**
 - Partielle spezielle Differenzierung:
> 50% NST-Komponente
und < 50% spezieller Tumortyp (Minorkomponente)
 - Gemischte Differenzierung:
> 50% spezieller Tumortyp
und < 50% NST-Komponente
Beispiel: Muzinöses Mamma-Ca, Mischtyp
 - Reine Typen:
> 90% des Tumors vom speziellen Typ
Beispiel: tubuläres oder kribriiformes Ca.

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

Befundung: Differenzierungsgrad

	Oxford		
	LoE	GR	AGO
■ Anwendung des Nottingham-Grading (Elston & Ellis 1991) für alle Typen des invasiven Mammakarzinoms	5	D	++
■ Bei sehr wenig Tumorgewebe rein nukleäres Grading oder Heranziehung zusätzlicher Kriterien wie Ki-67 Proliferationsfraktion	5	D	++
■ Grading des DCIS gemäß WHO-Klassifikation des Mammakarzinoms (4. Aufl., 2012)	5	D	++
■ Wiedergabe des Tumorggrading zumindest auch numerisch (z.B. 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.

Befundung: Differenzierungsgrad

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

Determination of tumor size

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

Multifocality

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

Oncology. 2008 Apr 1;19(4):614–22.

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.

Befundung: pTNM

Oxford		
LoE	GR	AGO
5	D	++

- **Anwendung der aktuellen UICC-Klassifikation (7. Auflage)**
 - pT 1–3:** Größter invasiver Tumorherd, nicht Gesamtausdehnung
 - pT4:** Alleinige Infiltration der Dermis nicht ausreichend. Kriterien für pT4a/b/c/d müssen erfüllt sein
 - pT4d:** Eine negative Hautbiopsie schließt pT4d (inflammatorisches Karzinom) nicht aus
 - pM:** pM1 bei jeglichem nicht regionärem Tumornachweis, ausgenommen kontralateralem Zweitkarzinom. Eine Angabe von MX wird nicht empfohlen.

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

Befundung: Beurteilung der Resektionsränder, R-Klassifikation

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

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

Befundung: Lymphgefäßinvasion

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

Oxford		
LoE	GR	AGO
5	D	++
3b	C	-
3b	C	++
5	D	+

Definition of L- and V-Classification

1. 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. Jet al. (2006). Distinguishing blood and lymph vessel invasion in breast cancer: a prospective immunohistochemical study. British Journal of Cancer, 94(11), 1643–1649.
4. Zaorsky, N. G., Patil, N., Freedman, G. M., et al. (2012). Differentiating lymphovascular invasion from retraction artifact on histological specimen of breast carcinoma and their implications on prognosis. Journal of Breast Cancer, 15(4), 478–480.

Prognostic significance of lymphovascular invasion

1. Gujam, F. J. A., Going, J. J., Edwards, J. et al. (2014). The role of lymphatic and blood vessel invasion in predicting survival and methods of detection in patients with

primary operable breast cancer. *Critical Reviews in Oncology/Hematology*, 89(2), 231–241. doi:10.1016/j.critrevonc.2013.08.014

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

Befundung: Evaluation tumor-infiltrierender Lymphozyten (TIL)

Oxford	LoE	GR	AGO
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- Identifikation von Tumoren mit prädominantem lymphozytären Infiltrat (> 50%) im Tumorstroma (n. Salgado et al.*)

5	D	+/-
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Nur das intratumorale Infiltrat im Stroma und nicht an der Invasionsfront berücksichtigen

Zentrale Fibrose- und Nekrosezonen nicht bewerten

Durchschnittswert des lymphozytären Infiltrates in Prozent angeben

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

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 immunology biomarker working group. *Mod Pathol*. 2016 Oct;29(10):1155-64
4. Loi, S., Sirtaine, N., Piette, Fet 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.

Befundung: nach neoadjuvanter Chemotherapie

	Oxford		
	LoE	GR	AGO
▪ Identifikation des Tumorbetts, sonst ypTX	4	D	++
▪ Angabe der Tumorgöße (max. Tumorbettgröße mit vitalem, invasiven Ca.)	4	D	++
▪ pCR definiert als Fehlen invasiven Karzinoms sowie Abwesenheit von Gefäßinvasion und Lymphknotenmetastasen. Vorhandensein von pTis ist anzugeben.	2b	D	+
▪ IHC zum Nachweis minimalen Residualtumors	4	D	+/-
▪ Angabe von ypTN-Status nach CHT	5	D	++
▪ Erneute Bestimmung der Hormonrezeptoren und des HER2-Status am Residualtumor	4	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.

Zusatzuntersuchungen: Bestimmung des ER mittels IHC

	Oxford		
	LoE	GR	AGO
■ Immunohistochemischer Nachweis am Paraffinschnitt	1a	A	++
■ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei $\geq 1\%$; niedrig positiv bei $\geq 1\%$ bis 9%)	1a	A	++
■ Angabe der Färbeintensität (0–3)	4	D	+
■ Allred Score (0–8), Remmele Score (0–12)	4	D	+
■ Reevaluation am Exzidat, wenn unklarer Befund an der Stanze oder triplenegativer Tumor	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
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

Zusatzuntersuchungen: Bestimmung des PgR mittels IHC

	Oxford		
	LoE	GR	AGO
▪ Immunohistochemischer Nachweis am Paraffinschnitt	1a	A	++
▪ Angabe des Prozentsatzes positiver Tumorzellkerne (positiv bei ≥ 10%)	1a	A	++
▪ Angabe der Färbeintensität (0–3)	4	D	+
▪ Allred Score (0–8), Remmele Score (0–12)	4	D	+

IHC-testing for PR-positivity

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

Zusätzliche Untersuchungen: Molekulare Bestimmung von ER/PgR

	Oxford		
	LoE	GR	AGO
▪ Bestimmung der Hormonrezeptoren auf Einzelgenebene durch validierte Genexpressions-Testkits	3b	A	+/-
▪ Bestimmung der Expression der Hormonrezeptoren durch RNA-Quantifizierung	5	D	-
▪ Verwendung der molekularen Rezeptorbestimmung zur Subtypisierung	3b	A	+

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

- 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
- 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
- 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
- Pentheroudakis, G., Kalogerias, 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.
- 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.
8. Fribbens C, O'Leary B, Kilburn L et al.. Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. *J Clin Oncol*. 2016;34:2961-2968. doi: 10.1200/JCO.2016.67.3061
9. Bartels S, Christgen M, Luft A, et al. Estrogen receptor (ESR1) mutation in bone metastases from breast cancer. *Mod Pathol*. 2018 Jan;31(1):56-61. doi: 10.1038/modpathol.2017.95.

Zusatzuntersuchungen: HER2-Bestimmung

	Oxford		
	LoE	GR	AGO
	1a	A	++
<ul style="list-style-type: none"> Immunohistochemie (IHC): <ul style="list-style-type: none"> HER2 + wenn starke komplette zirkuläre Membranfärbung von >10% invasiver Zellen (3+ Färbemuster) wenn > 10% zirkuläre, schwache/mäßige Membranfärbung oder ≤ 10% stark, U-förmig bei mikropapillären Ca (2+ Färbemuster): ISH erforderlich (CISH, SISH, FISH) 			
<ul style="list-style-type: none"> Einfarben In-Situ-Hybridisierung (ISH): HER2+ wenn ≥ 6 Signale in mindestens 20 kohäsiven Zellen, negativ bei < 4 Signalen/Kern 	3a	C	++
<ul style="list-style-type: none"> Zweifarben ISH: HER2+ bei Signal Ratio HER2:CEP17 ≥ 2,0 und/oder HER2-Signale > 6 	3a	C	++
<ul style="list-style-type: none"> Uneindeutiges Ergebnis (2+ IHC, ≥ 4–< 6 HER2 Signale ISH): Retestung mit anderer Methode oder an anderem Block 	3a	C	++
<ul style="list-style-type: none"> Validierung der Immunohistochemie an Stanzbiopsien 	5	D	++

- 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.
- 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
- 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.
- Jacobs T, Siziopikou K, Prioleau J et al. (1998) Do prognostic marker studies on core needle biopsy specimens of breast carcinoma accurately reflect the marker status of the tumor? Mod Pathol 11:259-264
- 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
- Wood B, Junckerstorff R, Sterrett G et al. (2007) A comparison of immunohistochemical staining for oestrogen receptor, progesterone receptor and HER-2 in breast core biopsies and subsequent excisions. Pathology 39:391-395
- 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

HER2-Bestimmung an Stanzbiopsien

Da eine Falschpositivität an Stanzbiopsien vorkommen kann (3+), sollte vor regelmäßiger HER2-Diagnostik an Stanzbiopsien eine Validierung der Methodik durch Parallelfärbung und Vergleich mit dem Resektat vorgenommen werden. Eine vermehrte Reaktivität des Stanzgewebes äußert sich an vermehrter Hintergrundfärbung, die durch den Vergleich mit normalem duktalem Epithel abgeschätzt werden sollte.

Alternativ oder zusätzlich können alle G1 und G2 Fälle mit HER2 3+ Befund in der Stanzbiopsie durch eine ISH oder eine Parallelbestimmung am Resektat überprüft werden.

Falschpositivität ist wahrscheinlich, wenn HER+ bei G1 Tumoren der folgenden histologischen Typen: infiltrierendes duktales or lobuläres Karzinom, ER und PgR positiv, tubulär, muzinös, kribriform, adenoid zystisches Karzinom (n. WHO)

Im Falle einer Diskrepanz zwischen Resektat und Stanzbiopsie sollte die Probe mit einer Überexpression einer ISH unterzogen werden. Sollte in einer der Proben eine Amplifikation sicher nachgewiesen sein, genügt das für eine eventuelle Indikationsstellung zur anti-HER2 spezifischen Therapie. Die zu erwartende Positivitätsrate liegt bei etwa 16% aller Fälle

Zusätzliche Untersuchungen: Molekulare Bestimmung von HER2

	Oxford		
	LoE	GR	AGO
▪ Therapieentscheidungen sollten nur auf IHC und ISH basieren	1a	A	++
▪ Bestimmung des HER2-Status durch validierte Genexpressions-Testkits	3b	B	+/-
▪ Bestimmung der HER2-Amplifikation durch NGS	5	D	-
▪ Verwendung der molekularen HER2-Bestimmung zur Subtypisierung	3b	B	+/-

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

1. Christgen, Matthias, Nadia Harbeck, Oleg Gluz, et al. "Recognition and Handling of Discordant Negative Human Epidermal Growth Factor Receptor 2 Classification by Oncotype DX in Patients with Breast Cancer.." Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 30, no. 26 (September 10, 2012): 3313–4–authorreply3314–5. doi:10.1200/JCO.2012.42.1990.
2. Dabbs, David J, Molly E Klein, Syed K Mohsin, et al. "High False-Negative Rate of HER2 Quantitative Reverse Transcription Polymerase Chain Reaction of the Oncotype DX Test: an Independent Quality Assurance Study.." Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 29, no. 32 (November 10, 2011): 4279–85. doi:10.1200/JCO.2011.34.7963.
3. 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
4. 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
5. Fountzilas, G., Valavanis, C., Kotoula, V., et al. (2012). HER2 and TOP2A in high-risk early breast cancer patients treated with adjuvant epirubicin-based dose-dense sequential chemotherapy. Journal of Translational Medicine, 10(1), 10. doi:10.1186/1479-5876-10-10
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Zusatzuntersuchungen: Ki-67 Bestimmung

	Oxford		
	LoE	GR	AGO
▪ Auszählung von Zellkernen an der Invasionsfront des Tumors	5	D	++
▪ Semiquantitative Schätzung oder Auszählen an Stanzbiopsaten	2	A	++
▪ Berücksichtigung auch schwach positiver Zellkerne	5	D	++
▪ Angabe des Ki-67 positiver Tumorzellen in Prozent	5	D	++
▪ Etablierung laborinterner Standards und Schwellenwerte	5	D	++
▪ Bildanalyse zur Objektivierung der Ki-67 Auszählung	5	D	+

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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Intrinsische Typen des Mammakarzinoms (molekulare und immunohistochemische Definitionen)

- Die sogenannten intrinsischen Typen (basal, luminal A/B-Typ, HER2) sind durch RNA-Expressionsprofile definiert. Es gibt zur Zeit keine allgemein akzeptierte Übertragung in Immunphänotypen, weder in Hinblick auf die notwendigen Marker noch die Schwellenwerte
- Unter praktischen Gesichtspunkten kann aber die Anwendung der Terminologie zur Beschreibung etablierter immunhistochemischer Untergruppen des Mammakarzinoms vertreten werden (ER/PR+ = luminal, HER2+ = HER2-Typ, triple negativ = basaler Typ)
- Der basale Typ weist eine 80% Überlappung mit der triple negativen Untergruppe des duktal invasiven Mammakarzinoms auf (ER <1% & PR <1% & Her2 0/1+/2+ (nicht-amplifiz., Ratio <2)
- Keiner der z.Zt. verfügbaren Marker (Ki-67, Grading, Recurrence Score etc.) kann zuverlässig zwischen den luminalen A and B Typen unterscheiden
- Auch RNA-Messungen sind zur Festlegung des intrinsischen Typs für therapeutische Zwecke nicht geeignet

Qualitätssicherung: Immunhistochemie

- **Verwendung einer automatisierten Färbepattform**
- **Teilnahme an Ringversuchen**
- **Strikte Einhaltung und Monitoring der Vorgaben für die Präanalytik (Fixation)**
- **Verwendung von On-Slide-Kontrollen**
- **Plausibilitätskontrollen (z.B. Tumortyp, Grading)**

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Qualitätssicherung: HER2-Bestimmung

- **Laufende Dokumentation der HER2-Befunde**
- **Qualitätsziel: HER2-Positivitätsrate 15% \pm 5%**
- **Verwendung standardisierter und validierter HER2-Testkits**
- **Teilnahme an Ringversuchen**

Qualitätssicherung: Befundung

- **Verantwortlichkeit der Befundung bei ein bis zwei in der Mammapathologie spezialisierten Pathologen**
- **Regelmäßige interdisziplinäre Befundbesprechungen mit radiologisch-pathologischer Korrelationsdiagnostik**
- **Teilnahme an Qualitätszirkeln**