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Pathology

Pathology

- **Versions 2004–2016:**
  Blohmer / Costa / Fehm / Friedrichs / Huober / Kreipe / Lück / Sinn / Thomssen

- **Version 2017:**
  Sinn / Schneeweiss

General Principles for Histopathologic Examination of Breast Cancer Specimens

- **Any statement in the histological report should reflect its clinical significance**
- **The terminology used is chosen according to current national guidelines and international classifications**
- **Quality control measures are required in all areas of diagnostic pathology**

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Preanalytics: Fixation

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

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Use of Fine Needle Aspiration Cytology*

	Oxford / LoE	GR	AGO
➢ Nipple secretion	5	D	+
➢ Tumor	5	D	-
➢ Cyst	5	D	+/-
➢ Lymph node	5	D	+/-

* Ultrasound-guided core biopsy recommended

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Workup: Macroscopy and Specimen Radiography

- **Consideration of preoperative imaging results (e.g. multifocality, intraductal component, adjacent structures) for sampling and documentation**
- **Routine documentation of macroscopic findings by using diagrams or macro image, with relation to topography**
- **Specimen radiography for non-palpable lesions and microcalcifications**

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Workup: Core Needle Biopsies (US-guided or stereotactic)

	Oxford / LoE	GR	AGO
➢ Routine workup in step sections (14G: 3 sections / 11G, 8G: 6–8 sections)	5	D	++
➢ Correlation with imaging (density, calcifications), use of B-classification	1b	B	++
➢ Frozen section diagnosis on core biopsies	5	D	- -
➢ Routine evaluation of ER/PgR and HER2 status	3b	C	++
➢ Turn-around time < 24 h (histology)	5	D	+

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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 in all dimensions	5	D	++
➢ Documentation after slicing using specimen radiography, photodocumentation or diagram	5	D	+

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References

Workup: Mastectomy Specimens

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

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Workup: Sentinel Node Biopsy

	Oxford / LoE	AGO / GR	
➢ Full workup using step sections of ≤ 500 µm on paraffin embedded tissue	5	D	++
➢ Cytokeratin immunohistochemistry			
- When suspicious, to detect micromet.	2b	B	++
- As a routine procedure	5	D	+/-
➢ Frozen section (invasive Ca.)			
- If clinical consequence	5	D	+
- If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BCT)	5	D	+/-
➢ Imprint cytology instead of, or in addition to frozen section	3b	C	+/-
➢ RT-PCR for epithelial genes	4	D	-
- OSNA	3b	B	-

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References

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Indications for Immediate Pathological Analysis Including Frozen Sections

	Oxford / LoE /GR		AGO
➢ **Sentinel node biopsy for invasive cancer**			
- If clinical consequence	**5**	**D**	**+**
- If no clinical consequence from frozen section (e.g. cT1 or cT2 and cN0 and BET)	**5**	**D**	**+/-**
➢ **Closest margin of resection**			
- If macroscopically < 1 cm	**5**	**D**	**+**
- If macroscopically > 1 cm	**5**	**D**	**-**
➢ **Lesions ≥ 1 cm, without core biopsy**	**5**	**D**	**+**
➢ **Non-palpable lesions or lesions < 1 cm**	**5**	**D**	**--**
➢ **Asservation of fresh tissue (tumor banking)**	**5**	**D**	**+**

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Further Information

References

Reporting: Histologic Tumor Type

	Oxford LoE / GR		AGO
➢ **Histologic tumor typing according to WHO-Classification, (4th ed., 2012)**	3b	C	++

- **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.

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Reporting: Grade of Malignancy

	Oxford LoE	Oxford 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 according to WHO-Classification, (4th ed., 2012)	5	D	++
➢ Reporting of tumor grading in numeric form (e.g. G3)	5	D	++

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Reporting: Tumor Size and Total Extent of Tumor

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

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References

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Reporting: pTNM

	Oxford LoE / GR	AGO
➢ Use of current UICC classifikation (7th ed.)	5 D	++

pT 1-3: Invasive tumor size (largest focus in case of multiplicity)

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 2nd primary contralaterally. Use of MX is not recommended.

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Further Information

References

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Reporting: Margins of Resection and R-Classification

	Oxford LoE	Oxford GR	AGO
➢ Evaluation of distance to all resection margins macroscopically and close margins histologically (< 1 cm)	5	D	++
➢ Reporting of minimal distance to resection margin and topography thereof	5	D	++
➢ R-Classification	5	D	++

R0: No residual tumor

R1: Microscopic invasive or noninvasive Carcinoma involving resection margin

RX: Presence of residual tumor cannot be assessed (e.g. tumor in multiple specimens)

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References

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Reporting: Lymphovascular Invasion

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

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Further Information

References

FORSCHEN
LEHREN
HEILEN

Reporting: Evaluation of Tumor-Infiltrating Lymphocytes (TIL)

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	Oxford LoE / GR		AGO
➢ **Identification of tumors with predominant lymphocytic infiltrate (> 50%) in tumor stroma (according to Salgado et al.*)**	**5**	**D**	**+/-**

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

Reporting: Evaluation after Neoadjuvant Chemotherapy

Guidelines Breast
Version 2017.1

	Oxford LoE	/ GR	AGO
➢ 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	4	D	+/-

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	++
➢ Staining intensity of pos. tumor nuclei (0 - 3)	4	D	+
➢ Allred Score (0 - 8), Remmele Score (0 - 12)	4	D	+
➢ Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy	5	D	+

For therapeutic implications see chapter "Endocrine therapy"

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Special Studies: PgR-Testing by IHC

	Oxford / LoE	AGO / GR	
➢ Immunohistochemical detection on paraffin embedded (FFPE) tissue	1a	A	++
➢ Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%)	1a	A	++
➢ Staining intensity of pos. tumor nuclei (0 - 3)	4	D	+
➢ Allred Score (0 - 8), Remmele Score (0 - 12)	4	D	+

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Additional Special Studies: Molecular Analysis of ER/PgR Status

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

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References

Special Studies: HER2 Testing

	Oxford / LoE / GR		AGO
➢ Reporting of immunohistochemistry (IHC): - HER2+ if strong complete circular membrane staining of > 10% invasive cells (3+ staining pattern) - if > 10% circular but moderate/weak membrane staining or ≤ 10% strong staining, U-shaped staining in micropapillary carcinoma (2+ staining pattern): ISH required (CISH, SISH, FISH)	1a	A	++
➢ Reporting of single-color In-Situ-Hybridisation (ISH): - HER2+ if signal counts ≥6 in at least 20 cohesive cells, negative if signal counts < 4 signals/nucleus	3a	C	++
➢ Reporting of dual-color ISH: - positive if signal ratio HER2:CEP17 ≥ 2,0 and/or HER2-signals ≥6	3a	C	++
➢ Equivocal results (2+ IHC, ≥4 - <6 HER2 signals ISH): Retest using other method and/or tissue block	3a	C	++
➢ Validation of immunohistochemistry on core biopsies	5	D	++

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HER2 Testing on Core Biopsies

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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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References

Additional Special Studies: Molecular Analysis of HER2 Status

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

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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	++
➢ 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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Further Information

References

Intrinsic Breast Cancer Types (Molecular and Immunohistochemical Definitions)

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- **Currently there is 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-labelling 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**

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%±5%**
- **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**

Pathology (2/30)

Further information:

This chapter contains basic recommendations for routine procedures in pathology. It is not intended to replace detailed protocols for the evaluation of operative specimens or for special studies. It is highly recommended to adhere to national quality assurance protocols concerning all aspects of working up and reporting of pathology specimens removed from women with breast cancer. Further information can be found in the following reports:

Screened data bases: PubMed 1970 – 2014

Guidelines screened:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- 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

References:

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2. Association of Directors of Anatomic and Surgical Pathology (1996). Recommendations for the reporting of breast carcinoma. Mod Pathol. 1996 Jan;9(1):77-81.
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8. Royal College of Pathologists (UK) (2005). NHSBSP guidelines for pathology reporting in breast disease. http://www.cancerscreening.nhs.uk/breastscreen/publications/nhsbsp58.html
9. 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

General principles for Histopathologic Examination of Breast Cancer Specimens (3/30))

No further information

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Preanalytics: Fixation (4/30)

No further information

References:

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Use of Fine Needle Aspiration Cytology (5/30)

No further information

References:

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Workup: Macroscopy and Specimen Radiography (6/30)

No further information

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Workup: Core Needle Biopsies (US-guided or stereotactic) (7/30)

No further information

References:

Statement: Routine workup in step sections

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Statement: Correlation with imaging

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Statement: Frozen section diagnosis on core biopsies

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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.
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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 of Breast-Conserving Specimens (8/30)

No further information

References:

1. Sinn HP, Anton HW, Magener A, von Fournier D, Bastert G, Otto HF.
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Workup of Mastectomy Specimens (9/30)

No further information

References:

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.
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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/

Workup: Sentinel Node Biopsy (10/30)

No further information

References:

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 ≥ 500 µm 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

2. Layfield et al. Intraoperative assessment of sentinel lymph nodes in breast cancer. The British journal of surgery (2011) vol. 98 (1) pp. 4-17
3. Limberis V, Romanidis C, Galazios G, Koutsougeras G, Papadopoulos N, Lambropoulou M, 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, J Henslee, G Huper, and JR Marks. "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, C S de Vries, S Shousha, H D Sinnett, E Nigar, et al. "Multicentre Evaluation of Intraoperative Molecular Analysis of Sentinel Lymph Nodes in Breast Carcinoma." *The British Journal of Surgery*, December 23, 2010.

Indications for Immediate Pathological Analysis Including Frozen Sections (11/30)

No further information

References:

Statement: Sentinel node biopsy for invasive cancer

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

Statement: Closest margin of resection

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

Statement: Lesions ≥ 1 cm, without core biopsy

1. Reiner-Concin A, Lax S. Mammakarzinom. In: Manual der gynäkologischen Onkologie (Reinthaler R, Helfer L, Hrsg.). http://www.ago-manual.at/inhalt/i-mammakarzinom/15-pathologie/
2. Fitzgibbons PL, Connolly JL, Page DL. Updated protocol for the examination of specimens from patients with carcinomas of the breast. Arch Pathol Lab Med 2000; 124:1026- 1033. (ACR)
3. Amendoeira I, Apostolikas N, Bellocq et al. Quality assurance guidelines for pathology: Open biopsy and resection specimens. In: Perry N, Broders M, de Wolf C, Törnberg S, Holland R, von Karsa L, Puthaar E (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.

Reporting: Histologic Tumor Type (12/30)

No further information

References:

WHO-Classifikation

1. Lebeau, A., Kriegsmann, M., Burandt, E., & Sinn, H. P. (2014). Invasive Mammakarzinome: Die aktuelle WHO classification. Der Pathologe, 35(1), 7–17.
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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

Reporting: Grade of Malignancy (13/30)

No further information

References:

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
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Grading of invasive lobular carcinoma

1. Rakha, E. A., El-Sayed, M. E., Menon, S., Green, A. R., Lee, A. H. S., & Ellis, I. O. (2007). Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. Breast Cancer Research and Treatment, 111(1), 121–127.

Reporting: Tumor Size and Total Extent of Tumor (14/30)

No further information

References:

Determination of tumor size

1. Pritt, B., Tessitore, J. J., Weaver, D. L., & Blaszyk, H. (2005). The effect of tissue fixation and processing on breast cancer size. Human Pathology, 36(7), 756–760.
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Multifocality

1. Hilton, J. F., Bouganim, N., Dong, B., Chapman, J. W., Arnaout, A., O'Malley, F. P., 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.
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Extensive intraductal component (EIC)

1. Mai, K. T., Perkins, D. G., & Mirsky, D. (2003). Location and extent of positive resection margins and ductal carcinoma in situ in lumpectomy specimens of ductal breast carcinoma examined with a microscopic three-dimensional view. The Breast Journal, 9(1), 33–38.
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Reporting: pTNM (15/30)

No further information

References:

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

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1. Wieland, A., Louwman, M., Voogd, A., van Beek, M., Vreugdenhil, G., & Roumen, R. (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]
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pT4d category: Inflammatory breast cancer

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Reporting: Margins of Resection and R-Classification (16/30)

No further information

References:

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
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R-Classifikation

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Reporting: Lymphovascular invasion (17/30)

No further information

References:

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., Cannizzaro, C., Falsirollo, F., Pollini, G. P., 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
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Prognostic significance of lymphovascular invasion

1. Gujam, F. J. A., Going, J. J., Edwards, J., Mohammed, Z. M. A., & McMillan, D. C. (2014). The role of lymphatic and blood vessel invasion in predicting survival and methods of detection in patients with primary operable breast cancer. Critical Reviews in Oncology/Hematology, 89(2), 231–241. doi:10.1016/j.critrevonc.2013.08.014
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Reporting: Evaluation of Tumor-Infiltating Lymphocytes (TIL) (18/30)

No further information

References:

Definition and impact of predominant lymphocytic infiltration

1. Salgado, R., Denkert, C., Demaria, S., Sirtaine, N., Klauschen, F., Pruneri, G., et al. (2014). The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Annals of Oncology.
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Reporting: Evaluation after Neoadjuvant Chemotherapy (19/30)

No further information

References:

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
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Special studies: ER-Testing by IHC (20/30)

No further information

References:

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., Burstein, H. J., Edge, S. B., Goldstein, L. J., 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
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IHC Scores

1. Allred, D. C., Harvey, J. M., Berardo, M., & Clark, G. M. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Modern Pathology, 11(2), 155–168.
2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) fur den immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

Monoclonal Antibodies for ER-Testing

1. Cheang MC, Treaba DO, Speers CH, Olivotto IA, Bajdik CD, Chia SK, Goldstein LC, Gelmon KA, Huntsman D, Gilks CB, Nielsen TO, Gown AM.
2. 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.
3. J Clin Oncol. 2006 Dec 20;24(36):5637-44.

Low ER+ Group (≥1%<10%)

1. Gloyeske, N. C., Dabbs, D. J., & Bhargava, R. (2014). Low ER+ Breast Cancer: Is This a Distinct Group? American Journal of Clinical Pathology, 141(5), 697–701.
2. Iwamoto, T., Booser, D., Valero, V., Murray, J. L., Koenig, K., Esteva, F. J., 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.

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Special studies: PgR-Testing by IHC (21/30)

No further information

References:

IHC-testing for PR-positivity

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

1. Braun, L., Mietzsch, F., Seibold, P., Schneeweiss, A., Schirmacher, P., Chang-Claude, J., et al. (2013). Intrinsic breast cancer subtypes defined by estrogen receptor signalling - prognostic relevance of progesterone receptor loss, 26(9), 1161–1171.
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Aberrant Expression of ER in triple negative breast cancer

1. Cserni, G., Francz, M., Kálmán, E., Kelemen, G., Komjáthy, D. C., Kovács, I., 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., Collins, L. C., Haibe-Kains, B., Tamimi, R. M., & Beck, A. H. (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., & Clark, G. M. (1998). Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Modern Pathology, 11(2), 155–168.
2. Remmele, W., & Stegner, H. (1987). Vorschlag zur einheitlichen Definition eines Immunreaktiven Score (IRS) fur den immunhistochemischen Ostrogenrezeptor-Nachweis (ER-ICA) im Mammakarzinomgewebe. Der Pathologe, 8(3), 138–140.

Additional special studies: Molecular analysis of ER/PgR status (22/30)

No further information

References:

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

1. Denkert, C., Huober, J., Loibl, S., Prinzler, J., Kronenwett, R., Darb-Esfahani, 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
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Quality assurance: HER2-Status (29/30)

No further information

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Quality assurance: Reporting (30/30)

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