Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Pathology

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

Guidelines screened


Antigen preservation


Retraction artifacts


Use of Breast Cytology*

<table>
<thead>
<tr>
<th>Nipple secretion</th>
<th>Tumor</th>
<th>Cyst</th>
<th>Lymph node</th>
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* Ultrasound-guided core biopsy recommended

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

- Routine workup in step sections (14G: 1–3 step sections / 11G, 8G: 6–8 step sections)
- Correlation with imaging (density, calcifications), use of B-classification
- Frozen section diagnosis on core biopsies
- Routine evaluation of ER/PR and HER2 status
- Turn-around time < 24 h (histology)

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<td>Routine workup in step sections</td>
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<td>Correlation with imaging (density, calcifications), use of B-classification</td>
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<td>Turn-around time &lt; 24 h (histology)</td>
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Statement: Routine workup in step sections


Statement: Correlation with imaging


Statement: Frozen section diagnosis on core biopsies


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


Statement: Turn-around time < 24h

Workup: Breast-Conserving Specimens

- Slicing perpendicular to the longitudinal axis (or perpendicular to the nipple-peripheral axis in case of spherical specimens)
  - Oxford: 5 D ++

- Systematic sampling, at least 1 tissue block every 1 cm
  - Oxford: 5 D ++

- Inking of resection margins. Sampling of resection margins
  - Oxford: 5 D ++

- Documentation after slicing using specimen radiography, photo documentation or diagram
  - Oxford: 5 D +

Guidelines


Systematic Sampling
Guidelines


Skin sparing and nipple sparing mastectomy


**Workup: Sentinel Node Biopsy**

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- **Full workup using step sections of ≥ 500 µm on paraffin embedded tissue**
- **Cytokeratin immunohistochemistry**
  - If suspicious, to detect micrometastases
  - For micrometastasis detection after NACT
  - As a routine procedure
- **Frozen section (compromises paraffin histomorphology)**
  - If clinical consequences
  - If no clinical consequences from frozen section (e.g., cT1 or cT2 and cN0 and cB0)
- **Imprint cytology instead of, or in addition to frozen section**
- **RT-PCR for epithelial genes**
  - OSNA

Statement: Evaluation of sentinel node biopsy


Statement: Full workup using step sections of ≥ 500 µm on paraffin embedded tissue


Statement: Frozen section

Statement: Imprint cytology instead or in addition of frozen section


Statement: RT-PCR for epithelial genes


Statement: Sentinel node biopsy for invasive cancer


Statement: Closest margin of resection


Statement: Lesions ≥ 1 cm, without core biopsy


Statement: Non-palpable lesions or lesions < 1 cm

WHO-Classification


Grading


2. WHO. Breast Tumours: WHO Classification of Tumours. 5 ed. Lyon (France): International Agency for Research on Cancer; 2019


Grading of invasive lobular carcinoma


Reporting: Tumor Size and Total Extent of Tumor

- **Reporting of invasive tumor size taking into account macroscopic and histologic findings and clinical imaging results**
  - Oxford LoE 5, GR D, AGO ++

- **Additional reporting of total extent of invasive carcinoma in case of satellite nodules or multifocality**
  - Oxford LoE 5, GR D, AGO ++

- **Reporting of size of non-invasive component (DCIS or LCIS) when DCIS or LCIS component is extensive (more than 2x invasive Ca)**
  - Oxford LoE 5, GR D, AGO ++

Determination of tumor size


Multifocality


**Extensive intraductal component (EIC)**


**Reporting: pTNM**

- Use of current UICC classification (8th ed.)
  - **pT1-3:** 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 2nd primary contralateral. Use of MX is not recommended.

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**TNM staging (7th ed.) according to UICC und AJCC**


**pT4b category: Involvemant of the skin**

pT4d category: Inflammatory breast cancer

Pathological margin assessment


R-Classifikation
Definition of L- and V-Classification


Detection of angioinvasion


Prognostic significance of lymphovascular invasion


Definition and impact of predominant lymphocytic infiltration


### Specimen processing after neoadjuvant chemotherapy


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

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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 if 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 (lymphnodes) | 2b | B | +/- |
| Reporting of ypTN after therapy | 5 | D | ++ |
| Repeat IHC for ER, PR, and HER2 | 5 | D | +/- |
| Intraoperative frozen section (reduced sensitivity) | 5 | D | - |
| Tumorregression-Scores: RCB-Score or Sataloff-Score | 4 | D | +/- |

**RCB-Score**


**Sataloff-Score**

**Special Studies:**

**ER-Testing by IHC**

- Immunohistochemical detection on paraffin embedded (FFPE) tissue
- Reporting percentage of pos. tumor nuclei (pos. if ≥ 10%, low pos. if ≥ 1%-10%)
- Staining intensity
- Only Allred Score (0–8) or Remmele Score (0–12)
- Re-evaluation on excision specimen if uncertain or triple-negative on core biopsy

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**ASCO/CAP Guideline for ER- and PR-testing**


**IHC-testing for ER-positivity**


IHC Scores


Monoclonal Antibodies for ER-Testing

Low ER+ Group


IHC-testing for PR-positivity


Prognostic significance


Aberrant Expression of ER in triple negative breast cancer


IHC Scores


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


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)

ASCO/CAP Guideline on HER2-Testing


IHC and molecular HER2-Testing


HER2-Analysis by ISH when IHC 2+

- **Single-Color In-Situ-Hybridisation (ISH):**
  - HER2+: if signal counts ≥ 6 in at least 20 cohesive cells
  - negative if signal counts < 4 signals/nucleus
  - 2-Color ISH recommended for ≥ 4 and < 6 signals/nucleus

- **Two-Color In-Situ-Hybridisation (ISH):**
  - Group 1: Ratio ≥ 2.0 and signals/nucleus ≥ 4.0 -> HER2+
  - Group 2: Ratio ≥ 2.0 and signals/nucleus < 4.0
  - -> HER2- (no benefit of anti-HER2 therapy)
  - Group 3: Ratio < 2.0 and signals/nucleus ≥ 6.0
  - -> HER2+ (but benefit of anti-HER2 therapy not certain)
  - Group 4: Ratio < 2.0 and signals/nucleus ≥ 4.0 und < 6
  - -> HER2- (no benefit of anti-HER2 therapy)
  - Group 5: Ratio < 2.0 und signals/nucleus < 4.0 -> HER2-

**ASCO/CAP Guideline on HER2-Testing**


**ISH HER2-Testing**


ASCO/CAP Guideline on HER2-Testing

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 PR 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

ASCO/CAP Guideline on HER2-Testing

Genomic and gene expression analysis of HER2


Ki-67 Methods and Reproducibility


**Impact of Ki-67 staining**


Ki-67 Image Analysis


Ki67 als dynamischer Marker nach Kurzzeit endokriner Therapie


BRCA 1/2


**PIK3CA**


**HER2-Mutation**


**ESR1**


NTRK


