Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar/Complex Sclerosing Lesion)
Lesions of Uncertain Malignant Potential (B3)

- **Versionen 2005–2022:**
  Albert / Audretsch / Bauerfeind / Brunnert / Ditsch / Fallenberg / Fersis / Friedrich / Friedrichs / Gerber / Huober / Kreipe / Maass / Nitz / Rody / Schmidt / Schreer / Sinn / Thomssen

- **Version 2023:**
  Kolberg-Liedtke / Reimer / Sinn
Pathology Reporting for Minimal Invasive Biopsies

B-Classification*

B1 = Unsatisfactory or normal tissue only
B2 = Benign lesion
B3 = Lesion of uncertain malignant potential
B4 = Suspicion of malignancy
B5 = Malignant
   B5a = Non-invasive
   B5b = Invasive
   B5c = In situ / invasion not assessable
   B5d = Non epithelial, metastatic

* AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.4, Juni 2021
1. **Lesions with increased risk of associated DCIS or invasive carcinoma**
   - Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of ductal type (classification possibly as B4, depending on extent of lesion)
   - Flat epithelial atypia (FEA)
   - Lobular neoplasia (LIN; LN; now subdivided into ALH and LCIS, no differentiation according to older nomenclature) classical and non-classical type
   - Atypical apocrine adenosis

2. **Potentially heterogeneous lesions with risk of incomplete sampling**
   - Cellular fibroepithelial lesion or phyllodes tumour without evidence of malignancy
   - Intraductal papilloma with / without atypia (possibly also B4, depending on the extent of the lesion)
   - Radial scar or complex sclerosing lesion (unless the radial scar only microscopically, not radiologically detected: B2)
   - Hemangioma

3. **Rare Lesions**
   - Adenomyoepithelioma, nipple adenoma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance
Management after Minimally Invasive Biopsy

- **Interdisciplinary conference:** Concordant findings in pathology and imaging?
  - yes: proceed according to histologic type and dimension of lesion
  - no: open biopsy

Vacuum-assisted biopsy (after core biopsy)

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Strategy after Diagnosis of ADH in Biopsy Sypcimen

ADH in core- / vacuum-assisted biopsy:

- Open excisional biopsy
- Open excisional biopsy may be omitted, if all following requirements apply:
  a) No mass-lesion radiologically, and
  b) a small lesion (≤ 2 TDLU*) in vacuum biopsy, and
  c) complete removal of imaging abnormality

ADH at margins in open biopsy specimen:

- No further surgery, if incidental finding accompanies invasive or intraductal carcinoma

* Terminal ductal-lobular unit

Oxford

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Lobular Intraepithelial Neoplasia (LIN)

- **Includes:**
  - Atypical lobular hyperplasia
  - Classical lobular carcinoma in situ (LIN, classical variant)
  - Non-Classical lobular carcinoma in situ (LIN, classical variant)

- LIN 1–3 classification is not sufficiently validated prognostically
- Non-Classical LIN (pleomorphic LIN, florid LIN) are classified as lesions with elevated risk → potentially B5a
- **Indicator / precursor lesion:**
  Ipsi- and contralaterally increased breast cancer risk: 7x after 10 years
**Upgrade rates* for B3 lesions**

* i.e., upgrade to malignant diagnosis when excised

<table>
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<tr>
<th>Risk lesion</th>
<th>Upgrade rate to in situ or invasive Ca</th>
<th>References</th>
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<tbody>
<tr>
<td>Atypical lobular hyperplasia (ALH)</td>
<td>5%</td>
<td>[1]</td>
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<tr>
<td>Classical lobular neoplasia (C-LCIS)</td>
<td>4 - 16%</td>
<td>[1-3]</td>
</tr>
<tr>
<td>Non-classical lobular neoplasia (pleomorphic, florid LCIS, NC-LCIS)</td>
<td>33 - 39%</td>
<td>[3, 4]</td>
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<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>23%</td>
<td>[1]</td>
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<tr>
<td>Flat epithelial atypia (FEA)</td>
<td>0 - 14%</td>
<td>[5, 6]</td>
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<tr>
<td>Papilloma</td>
<td>12%</td>
<td>[7]</td>
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<tr>
<td>- no atypia</td>
<td>6 - 10%</td>
<td>[7, 8]</td>
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<tr>
<td>- atypia</td>
<td>21 -29%</td>
<td>[8, 9]</td>
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<tr>
<td>Radial scar or complex sclerosing lesion</td>
<td>7 - 11%</td>
<td>[10-12]</td>
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<tr>
<td>- no atypia</td>
<td>5%</td>
<td>[12]</td>
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<tr>
<td>- atypia</td>
<td>25%</td>
<td>[13]</td>
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## Risk of malignant disease during follow-up*

* i.e. ipsilateral or contralateral disease irrespective of localization of prior lesion

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<tr>
<th>Risk lesion</th>
<th>Upgrade rate to in situ or invasive Ca</th>
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<tr>
<td>LIN</td>
<td>7x / 10 yrs (ipsi-/contralateral)</td>
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<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
<td>3-5x / 10 years (ipsi-/contralateral)</td>
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<tr>
<td>Papilloma</td>
<td></td>
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<tr>
<td>• no atypia</td>
<td>4.6% (ipsilateral)</td>
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<tr>
<td>• atypia</td>
<td>13% (ipsilateral)</td>
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LIN with elevated risk

- **Non-classical LCIS:**
  - Pleomorphic LCIS: high-grade cellular atypia, common involvement of ducts with comedo necrosis and microcalcifications
  - Florid LCIS: involvement of multiple lobuli with a maximum extension until confluence and involvement of ductuli and neighboring TDLU

- **Microinvasion in classical and non-classical LCIS***:
  - classical LCIS: n = 11
  - florid LCIS: n = 4
  - pleomorphic LCIS: n = 1

Microinvasion in 0.37% of all LCIS (n = 4310) and in 0.43% among all invasive lobular breast cancers (n = 3740).

Strategy after Diagnosis of LIN

- LIN in core- / vacuum-assisted biopsy:
  - No further measures if LIN (LCIS, classical variant) with involvement of ≤ 3 TDLU (terminal ductulo-lobular unit) in vacuum biopsy and concordant with imaging.  
  - Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings.

- LIN at margins of resection specimen (BCT):
  - No further surgery.

Exceptions:
  a) Pleomorphic LIN, florid LIN, or LIN with necrosis
  b) Imaging abnormality is not removed
# Strategy after Diagnosis of FEA

## FEA in core biopsy / vacuum-assisted biopsy:

- **Open excisional biopsy**
  - **LoE**: 2b
  - **GR**: B
  - **AGO**: +

- **Open excisional biopsy may be omitted under the following circumstances:**
  1. a small lesion (≤ 2 TDLU* in vacuum biopsy)
  2. Complete or near complete removal of imaging abnormality

- **LoE**: 2b
- **GR**: B
- **AGO**: +

## FEA at margins in resection specimen:

- **No further surgery, unless calcifications have not been completely removed**

- **LoE**: 3b
- **GR**: C
- **AGO**: ++

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* TDLU = Terminal ductal-lobular unit
**Papilloma**

- **Includes**: Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be **distinguished from** peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be distinguished from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Precursor lesion**: May be associated with in-situ or invasive cancer (up to 6% without atypia if concordant imaging, up to 30% with atypia), increased ipsilateral risk for cancer (up to 4.6% and up to 13% in case of atypical papilloma).
Strategy after Diagnosis of Papilloma

- Papilloma without atypia in core needle or vacuum biopsy:
  - no further therapy, if biopsy sufficiently representative (100mm³) and concordant with imaging
    
- Multiple papillomas (>2 mm)
  - open biopsy

- Papilloma with atypia in core needle or vacuum biopsies:
  - open biopsy

- Papilloma at resection margin:
  - no published data available

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Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radial configuration.
- Includes:
  - radial scar (usually ≤ 1 cm)
  - complex sclerosing lesion (> 1 cm)
- Additional risk factor in patients with benign epithelial hyperplasia (proliferating breast disease)
- Risk for upgrade in open biopsy after diagnosis of a radial sclerosing lesion, depending on the size of the needle (CNB) or method (VAB) and additional atypia: 1–18%
Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

- Radial scar / CSL in core- / vacuum-assisted biopsy:
  - Open excisional biopsy
    - Without atypia
    - With atypia
  → Omission of open excisional biopsy if small (< 5mm) lesion or (near) complete removal of imaging abnormality
  
- Radial scar / CSL at margins in resection specimen:
  → No further surgery

Oxford

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Breast Cancer Early Detection: Follow-up Imaging for Women Age 50–69 Years with B3-Lesions

- **FEA, non-atypical papilloma, radial sclerosing lesion**
  - Screening mammography
  - Oxford
    - LoE: 5
    - GR: C
    - AGO: ++

- **LIN**
  - Mammography (12 months)
  - Oxford
    - LoE: 3a
    - GR: C
    - AGO: ++

- **ADH**
  - Mammography (12 months)
  - Oxford
    - LoE: 3a
    - GR: C
    - AGO: ++

Women with LIN and ADH should be informed about their elevated risk of breast cancer.
Medical Prevention for B3-Lesions With Increased Risk of Associated DCIS or Invasive Carcinoma

- Tamoxifen 20 mg/d (5 yrs) for women > 35 years
  - Oxford
    - LoE: 1a
    - GR: A
    - AGO: +/-

- Low-dose Tamoxifen 5 mg/d* (3 years) independent of menopausal status
  - Oxford
    - LoE: 2b
    - GR: B
    - AGO: +/-

- Aromatase inhibitors (Exemestane, Anastrozole) for postmenopausal women
  - Oxford
    - LoE: 1b
    - GR: A
    - AGO: +/-

- Raloxifen for postmenopausal women: Risk reduction of invasive BC only
  - Oxford
    - LoE: 1b
    - GR: A
    - AGO: +/-**

Medical prevention should only be offered after individual and comprehensive counseling; overall benefit depends on classification, age, and pre-existing conditions that may influence occurrence of side effects.

* 5 mg Tablet not available; alternatively 10 mg p.o. q2d

** Risk situation as defined in NSABP P1-trial (1.66% in 5 years)