Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)
Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Versions 2005–2020:**
  Albert / Audretsch / Brunnert / Ditsch / Fallenberg / Fersis / Friedrich / Friederichs / Gerber / Huober / Kreipe / Nitz / Rody / Schmidt / Schreer / Sinn / Thomssen

- **Version 2021:**
  Kreipe / Maass
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

* National Coordinating Group for Breast Screening Pathology (NHSBSP), E.C. Working Group on Breast Screening Pathology, S3-Leitlinie Mammakarzinom der DKG

Lesions of Uncertain Malignant Potential (B3)
B3-Lesions

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, 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 3a C ++
  - no: open biopsy 3a C ++

Vacuum-assisted biopsy (after core biopsy) 5 D +
Atypical ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal epithelial proliferation (AIDEP), atypical epithelial proliferation of ductal type
- **Definition:** Atypical intraductal proliferations with cytological and structural features of well differentiated DCIS, such as rigid bridging or micropapillae, well demarcated cell borders and occupy less than two separate duct spaces. The extension of all involved lumens within one ductulo-lobular unit is less than 2 mm. Atypical ductal proliferations larger than 2 mm or in at least two ductules are classified as DCIS (low-grade).
- **Indicator/Precursor lesion:** Ipsilateral- and contralateral breast cancer risk: RR 3 - 5 x after 3 - 5 years.
- Particularly high risk for breast cancer when combined with BIRADS IV / V and high breast volume.
Strategy after Diagnosis of ADH in Biopsy Specimen

ADH in core- / vacuum-assisted biopsy:

- Open excisional biopsy
- Open excisional biopsy may be omitted, if:
  - 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

Lesions of Uncertain Malignant Potential (B3)

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Oxford

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<thead>
<tr>
<th>LoE</th>
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<tbody>
<tr>
<td>3a</td>
<td>C</td>
<td>++</td>
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<tr>
<td>5a</td>
<td>C</td>
<td>+/-</td>
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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 premalignant → **B5a**

- **Indicator/Precursor lesion:**
  Ipsilateral and contralaterally increased breast cancer risk:
  7 x after 10 years
Classical LIN and Variants of LIN (non-classical LCIS)

Classical LIN

LIN with comedo type necrosis

Florid LIN

Pleomorphic LIN
LIN with High Risk

- Non-Classical LCIS:
  - Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necrosis, microcalcifications
  - Florid LCIS: Involvement of numerous lobuli with distension and near confluence, extension to ductules and neighboring TDLU

- LCIS with microinvasion*:
  - classical LCIS: $n = 11$
  - florid LCIS: $n = 4$
  - pleomorphic LCIS: $n = 1$

## Strategy after Diagnosis of LIN

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<tbody>
<tr>
<td>LIN in core- / vacuum-assisted biopsy:</td>
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<tr>
<td>§ No further measures if LIN (LCIS, classical variant) with involvement of ≤ 3 TDLU (terminal ductulo-lobular unit) in vacuum biopsy and concordant with imaging</td>
<td>2b</td>
<td>C</td>
<td>++</td>
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<tr>
<td>§ Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings</td>
<td>2b</td>
<td>C</td>
<td>++</td>
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<td>LIN at margins of resection specimen (BCT):</td>
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<tr>
<td>§ No further surgery</td>
<td>2a</td>
<td>C</td>
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**Exceptions:**

a) Pleomorphic LIN, florid LIN, or LIN with necrosis

a) Imaging abnormality is not removed
Flat Epithelial Atypia (FEA)

- **Synonyms:** Columnar cell hyperplasia with atypia, columnar cell metaplasia with atypia, ductal intraepithelial neoplasia grade 1A (DIN 1A)

- **Differential diagnosis:**
  - ADH is discriminated by architectural features (micropapillary, cribriform) → **B3**
  - Clinging carcinoma is discriminated by high grade nuclear atypia (G2/G3) and classified as ductal carcinoma in situ → **B5a**

- **Marker lesion:**
  FEA frequently is associated with calcifications and may be associated with low-grade intraductal carcinoma. Frequent occurrence in combination with high density of the breast (OR1.3). High risk for associated breast cancer in the presence of extensive calcifications (also when 75% of calcification remained after biopsy), age > 57J, > 1 cm in imaging, > = 4 foci.
Strategy after Diagnosis of FEA

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

**FEA at margins in resection specimen:**
- No further surgery, unless calcifications have not been completely removed

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* TDLU = Terminal ductal-lobular unit

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<tr>
<td></td>
<td>3b</td>
<td>C</td>
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<td></td>
<td>5</td>
<td>C</td>
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Lesions of Uncertain Malignant Potential (B3)

- **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 (100 mm$^2$) and concordant with imaging
  - Oxford: 3a, C, +

- Multiple papillomas
  - open biopsy
  - Oxford: 3a, C, ++

- Papilloma with atypia in core needle or vacuum biopsies:
  - open biopsy
  - Oxford: 3a, C, ++

- Papilloma at resection margin:
  - no published data available
  - Oxford: 3a, C, +

Lesions of Uncertain Malignant Potential (B3)
Radially Sclerosing Lesion

- Benign pseudoinfiltrative lesion with central fibroelastic core and radical configuration.

- Includes:
  - radial scar
  - 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 may be omitted with a small (< 5mm) lesion or complete removal or near complete removal of imaging abnormality

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<tr>
<td></td>
<td>5a</td>
<td>C</td>
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- **Radial scar / CSL at margins in resection specimen:**
  - No further surgery

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Management Radial Scar

- “When RS (radial scar) is associated to atypia (such as flat epithelial atypia (FEA), atypical ductal (ADH), or lobular neoplasia (classical LN)), management can the same as recommended in cases of atypia alone.”

Follow-up Imaging for Women Age 50–69 Years with B3-Lesions

<table>
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<th>Lesion Type</th>
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<tr>
<td><strong>FEA, non-atypical papilloma</strong></td>
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<tr>
<td>Screening mammography</td>
<td>5</td>
<td>C</td>
<td>++</td>
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<tr>
<td><strong>LIN</strong></td>
<td></td>
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<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
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<tr>
<td><strong>ADH</strong></td>
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<td></td>
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<tr>
<td>Mammography (12 months)</td>
<td>3a</td>
<td>C</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Women with LIN and ADH should be informed about their elevated risk of breast cancer</td>
<td>3a</td>
<td>C</td>
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Medical Prevention for Lesions with Uncertain Biological Behavior (incl. LIN, ADH)

- **Tamoxifen for women > 35 years**
  - Oxford: 1a, A, +/-

- **Low-dose Tamoxifen 5mg (3 years)**
  - Oxford: 2b, B, +/-

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

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

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.

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

- 500 women ≤ 75 with intraepithelial neoplasia (ADH, LCIS, DCIS)
- Tamoxifen 5 mg/d for 3 years vs. placebo
- Breast cancer events: 14 vs. 28
  - invasive: 11 vs. 19
  - HR 0.48; 95% CI 0.26-0.92; P = 0.02
- NNT 22
- PROM comparable except for hot flushes

DeCensi et al. J Clin Oncol 37:1629-1637, 2019
Lesions of Uncertain Malignant Potential (B3)
## Tamoxifen Chemoprevention—End of the Road?

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<tr>
<th></th>
<th>Placebo</th>
<th>Verum</th>
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<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>18.322</td>
<td>18.355</td>
</tr>
<tr>
<td><strong>Invasive breast cancer</strong></td>
<td>805</td>
<td>537</td>
</tr>
<tr>
<td><strong>ER-positive</strong></td>
<td>632</td>
<td>350</td>
</tr>
<tr>
<td><strong>ER-negative</strong></td>
<td>144</td>
<td>173</td>
</tr>
<tr>
<td><strong>Breast cancer-related death</strong></td>
<td>48</td>
<td>60</td>
</tr>
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Narod. JAMA Oncol 1:1033-4, 2015