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

Pubmed 2010-2020 queries

Lobular neoplasia (114 Results)

Atypical ductal hyperplasia (71 Results)

Flat epithelial atypia (45 Results)
Papilloma (183 Results)

Radial scar (17 Results)

**National and international guidelines**

1. AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.0, Aktualisierung 2017 http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/


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

1. AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.0, Aktualisierung 2017 http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/


Lesions of Uncertain Malignant Potential (B3)

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, mucocle-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
  - no: open biopsy

  Vacuum-assisted biopsy (after core biopsy)

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<tr>
<th>Oxford</th>
<th>LoE</th>
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<td>3a</td>
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<td></td>
<td>5</td>
<td>D</td>
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2. AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 4.0, Aktualisierung 2017 http://www.leitlinienprogramm- onkologie.de/leitlinien/mammakarzinom/
8. Neal L, Sandhu NP, Hieken TJ et al.: Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on


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:** ipsi- 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.


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


Statement: Indicator-/precursor lesion


Statement: Pleomorphic lobular carcinoma in situ (PLCIS)


**Statement: Florid lobular carcinoma in situ (FLCIS)**

**Statement: Lobular carcinoma in situ with microinvasion**
**Strategy after Diagnosis of LIN**

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<tr>
<td>LIN in core- / vacuum-assisted biopsy:</td>
<td>2b</td>
<td>C</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>
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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>
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<tr>
<td>LIN at margins of resection specimen (BCT):</td>
<td>2a</td>
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<tr>
<td>- No further surgery</td>
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<td>Exceptions:</td>
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<tr>
<td>a) Pleomorphic LIN, florid LIN, or LIN with necrosis</td>
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<tr>
<td>b) Imaging abnormality is not removed</td>
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**LIN in core- / vacuum-assisted biopsy (LoE 2b)**


Lesions of Uncertain Malignant Potential (B3)


**LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a)**


*Lesions of Uncertain Malignant Potential (B3)*
### 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 > 57, > 1 cm in imaging, > 4 foci.

### General


Statement: Marker Lesion


Lesions of Uncertain Malignant Potential (B3)


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).


35. Polat DS, Knippa EE, Ganti R et al. Benign breast papillomas without atypia diagnosed with core needle biopsy: Outcome of surgical 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%


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

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

- Tamoxifen for women > 35 years
  - Oxford LoE: 1a, GR: A, AGO: +/-
- Low-dose Tamoxifen 5mg (3 years)
  - 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.

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

8. Lazzeroni M, Puntoni M, Provinciali N et al.: Estimating the magnitude of clinical benefit of systemic therapy in patients with DCIS or...


# Tamoxifen Chemoprevention—End of the Road?

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