

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN / LCIS, FEA, Papilloma, Radial Scar / Complex
Sclerosing Lesion)

Lesions of Uncertain Malignant Potential (B3)

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- **Versions 2005-2024:**

**Albert / Audretsch / Bauerfeind / Brunnert / Ditsch / Fallenberg / Fersis /
Friedrich / Friedrichs / Gerber / Huober / Kolberg-Liedtke / Kreipe /
Maass / Nitz / Reimer / Rody / Schmidt / Schreer / Sinn / Thomssen**

- **Version 2025:**

Kreipe / Sinn / Solbach

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

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 intraepithelial neoplasie (LIN; LN), divided in atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS, 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

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- **Interdisciplinary conference:
Correlation between imaging and pathology**
 - **concordant**
proceed according to histologic type and dimension
of lesion
 - **discordant**
 - **open biopsy**
 - **representative vacuum-assisted biopsy (after
core biopsy)**

3a

C

++

3a

C

++

4

C

+

Strategy after Diagnosis of ADH in Biopsy Specimen

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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

3a	C	++
5	C	+/-

ADH at margins in open biopsy specimen:

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

3a	C	+
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* TDLU = Terminal ductal-lobular unit

Lobular Intraepithelial Neoplasia (LIN, LN)

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Definitions:

- **Atypical lobular hyperplasia = less than 50% atypical lobular cells = B3**
- **Classical lobular carcinoma in situ (classical LCIS) = B3**
ipsi- and contralaterally increased breast cancer risk:
7fold after 10 years
- **Non-classical lobular carcinoma in situ (non-classical LCIS): pleomorphic LCIS and florid LCIS (LIN3 according to older terminology)**
elevated local risk → potentially B5a
- **Subclassification into LIN 1-3 is not sufficiently validated prognostically and has been abandoned**

Upgrade Rates* for B3 Lesions

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

Risk lesion	Upgrade rate to in situ or invasive Ca	References
Atypical lobular hyperplasia (ALH)	5%	[1]
Classical LCIS	4-16%	[1-3]
Non-classical LCIS (pleomorphic LCIS, florid LCIS)	33-44%	[3, 4; 17]
Atypical ductal hyperplasia (ADH)	23-36%	[1, 16]
Flat epithelial atypia (FEA)	0-14%	[5, 6]
Papilloma	12-19%	[7, 16]
- no atypia	6-10%	[7, 8, 10, 11]
- atypia	21-29%	[8, 9]
Radial scar or complex sclerosing lesion	7-11%	[12-16]
- no atypia	5%	[14]
- atypia	25%	[15]

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Strategy after Diagnosis of LIN / LCIS

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■ LIN / LCIS 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 / LCIS, florid LIN / LCIS, or LIN / LCIS with comedo type necrosis or if not concordant with imaging findings.

2b C ++

2b C ++

■ LIN / LCIS at margins of resection specimen (BCT):

- No further surgery.

2a C ++

Exceptions:

- a) Pleomorphic, florid, or LIN / LCIS with necrosis
- b) Imaging abnormality is not removed

Strategy after Diagnosis of FEA

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

- | | | | |
|--|----|---|---|
| <ul style="list-style-type: none"> ■ Open excisional biopsy | 2b | B | + |
| <ul style="list-style-type: none"> ■ Open excisional biopsy may be omitted under the following circumstances: <ul style="list-style-type: none"> a. a small lesion (≤ 2 TDLU* in vacuum biopsy) <u>and</u> b. Complete or near complete removal of imaging abnormality | 2b | B | + |

- **FEA at margins in resection specimen:**

- | | | | |
|--|----|---|----|
| <ul style="list-style-type: none"> ■ No further surgery, unless calcifications have not been completely removed | 3b | C | ++ |
|--|----|---|----|

* TDLU = Terminal ductal-lobular unit

Papilloma

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- **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

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|--|-----|----|-----|
| <ul style="list-style-type: none"> Papilloma without atypia in core needle or vacuum biopsy: <ul style="list-style-type: none"> → no further therapy, if biopsy sufficiently representative and concordant with imaging | 2b | C | + |
| <ul style="list-style-type: none"> Multiple papillomas (> 2 mm) <ul style="list-style-type: none"> → open biopsy | 3a | C | ++ |
| <ul style="list-style-type: none"> Papilloma with atypia in core needle or vacuum biopsies: <ul style="list-style-type: none"> → open biopsy | 3a | C | ++ |
| <ul style="list-style-type: none"> Papilloma at resection margin: <ul style="list-style-type: none"> → no published data available | | | |

Radial Sclerosing Lesion

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- **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)

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<ul style="list-style-type: none"> ■ Radial scar / CSL in core- / vacuum-assisted biopsy: <ul style="list-style-type: none"> ■ Open excisional biopsy <ul style="list-style-type: none"> ■ Without atypia ■ With atypia → Omission of open excisional biopsy if small (< 5 mm) lesion or (near) complete removal of imaging abnormality ■ Radial scar / CSL at margins in resection specimen: <ul style="list-style-type: none"> → No further surgery 	<p>3a</p> <p>3a</p> <p>3a</p> <p>4</p> <p>3b</p>	<p>C</p> <p>C</p> <p>C</p> <p>C</p> <p>C</p>	<p>+</p> <p>+</p> <p>++</p> <p>+</p> <p>++</p>

Breast Cancer Early Detection: Follow-up Imaging for Women Age 50-75 Years with B3-Lesions

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<ul style="list-style-type: none"> ■ FEA, non-atypical papilloma, radial scar, complex sclerosing lesion <ul style="list-style-type: none"> ■ Screening mammography 	5	C	++
<ul style="list-style-type: none"> ■ LIN / LCIS <ul style="list-style-type: none"> ■ Mammography (12 months) 	3a	C	++
<ul style="list-style-type: none"> ■ ADH <ul style="list-style-type: none"> ■ Mammography (12 months) 	3a	C	++
Women with LIN / LCIS and ADH should be informed about their elevated risk of breast cancer	3a	C	++

Medical Prevention for Patients with Increased Risk of DCIS or Invasive Carcinoma



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▪ Tamoxifen 20 mg/d (5 yrs) for women > 35 years	1a	A	+/-
▪ Low-dose Tamoxifen 5 mg/d* (3 years) independent of menopausal status	1b	B	+/-
▪ Aromatase inhibitors (Exemestane, Anastrozole) for postmenopausal women	1a	A	+/-
▪ Raloxifen for postmenopausal women: Risk reduction of invasive BC only	1a	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.

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

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