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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)



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## Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Versions 2005–2021:**  
**Albert / Audretsch / Brunnert / Ditsch / Fallenberg / Fersis / Friedrich /  
Friedrichs / Gerber / Huober / Kreipe / Maass / Nitz / Rody / Schmidt /  
Schreer / Sinn / Thomssen**
- **Version 2022:**  
**Bauerfeind / Kreipe**

### Pubmed 2010-2021 queries

#### Lobular neoplasia (114 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2012/01/01"[dp] : "2020/01/01"[dp]) AND ("lobular neoplasia"[ti] OR "lobular intraepithelial neoplasia"[ti] OR "atypical lobular hyperplasia"[ti] OR "lobular carcinoma in situ"[ti] OR "LIN"[ti] OR "ALH"[ti] OR "LCIS"[ti]) AND ("english"[la] OR "german"[la])

#### Atypical ductal hyperplasia (71 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2012/01/01"[dp] : "2020/01/01"[dp]) AND ("atypical ductal hyperplasia"[ti] OR "atypical hyperplasia"[ti] OR "ADH"[ti]) AND ("english"[la] OR "german"[la])

#### Flat epithelial atypia (45 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast

Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2012/01/01"[dp] : "2020/01/01"[dp]) AND ("flat epithelial atypia"[ti] OR "columnar cell"[ti] OR "FEA"[ti]) AND ("english"[la] OR "german"[la])

#### Papilloma (183 Results)


(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2012/01/01"[dp] : "2020/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[Title]

#### Radial scar (17 Results)

(Breast Diseases/CL[mh] OR Breast Diseases/DI[mh] OR Breast Diseases/EP[mh] OR Breast Diseases/GE[mh] OR Breast Diseases/MO[mh] OR Breast Diseases/PA[mh] OR Breast Diseases/RT[mh] OR Breast Diseases/SU[mh] OR Breast Diseases/TH[mh]) AND ("2012/01/01"[dp] : "2020/01/01"[dp]) AND ("radial scar"[ti] OR "complex sclerosing lesion"[ti] OR "radial sclerosing lesion"[ti]) AND ("english"[la] OR "german"[la])

#### National and international guidelines

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2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast cancer. Version 1. 2020.
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## Pathology Reporting for Minimal Invasive Biopsies

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### 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. The Royal College of Pathologists. Guidelines for non-operative diagnostic procedures and reporting in breast cancer [Internet]. United Kingdom: National ...; 2016. Available from: <https://www.rcpath.org/profession/publications/cancer-datasets.html>
2. Ellis IO, Humphreys S, Michell M et al. Best Practice No 179. Guidelines for breast needle core biopsy handling and reporting in breast screening assessment. Vol. 57, Journal of clinical pathology. 2004. pp. 897–902.
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 <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2022.1E  www.ago-online.de</p>	<h2 style="text-align: center; color: green;">B3-Lesions</h2> <ol style="list-style-type: none"> <li><b>1. Lesions with increased risk of associated DCIS or invasive carcinoma</b> <ul style="list-style-type: none"> <li>▪ Atypical ductal hyperplasia (ADH) or atypical epithelial proliferation of ductal type (classification possibly as B4, depending on extent of lesion)</li> <li>▪ Flat epithelial atypia (FEA)</li> <li>▪ Lobular neoplasia (LIN; LN; now subdivided into ALH and LCIS, no differentiation according to older nomenclature) classical and non-classical type</li> <li>▪ Atypical apocrine adenosis</li> </ul> </li> <li><b>2. Potentially heterogeneous lesions with risk of incomplete sampling</b> <ul style="list-style-type: none"> <li>▪ Cellular fibroepithelial lesion or phyllodes tumour without evidence of malignancy</li> <li>▪ Intraductal papilloma with / without atypia (possibly also B4, depending on the extent of the lesion)</li> <li>▪ Radial scar or complex sclerosing lesion (unless the radial scar only microscopically, not radiologically detected: B2)</li> <li>▪ Hemangioma</li> </ul> </li> <li><b>3. Rare Lesions</b> <ul style="list-style-type: none"> <li>▪ Adenomyoepithelioma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance</li> </ul> </li> </ol>
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11. Bachert S, Jen S, Denison C et al. :Breast lesions associated with mammographic architectural distortion: a study of 588 core needle biopsies Dec 29. 2021 doi: 10.1038/s41379-021-00996-3. Online ahead of print.



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## Management after Minimally Invasive Biopsy


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<ul style="list-style-type: none"> <li>▪ <b>Interdisciplinary conference: Concordant findings in pathology and imaging?</b></li> </ul>			
<ul style="list-style-type: none"> <li>▪ <b>yes: proceed according to histologic type</b></li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>▪ <b>no: open biopsy</b></li> </ul>	3a	C	++
Vacuum-assisted biopsy (after core biopsy)	5	D	+

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Mod Pathol





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## 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.


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Strategy after Diagnosis of ADH in Biopsy Specimen			
	Oxford		
	LoE	GR	AGO
<b>ADH in core- / vacuum-assisted biopsy:</b>			
▪ <b>Open excisional biopsy</b>	3a	C	++
▪ <b>Open excisional biopsy may be omitted, if:</b>	5a	C	+/-
a) No mass-lesion radiologically, and			
b) a small lesion ( $\leq 2$ TDLU*) in vacuum biopsy, and			
c) complete removal of imaging abnormality			
<b>ADH at margins in open biopsy specimen:</b>			
▪ <b>No further surgery, if incidental finding accompanies invasive or intraductal carcinoma</b>	3a	C	++
* Terminal ductal-lobular unit			

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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:  
Ipsi- and contralaterally increased breast cancer risk:  
7 x after 10 years

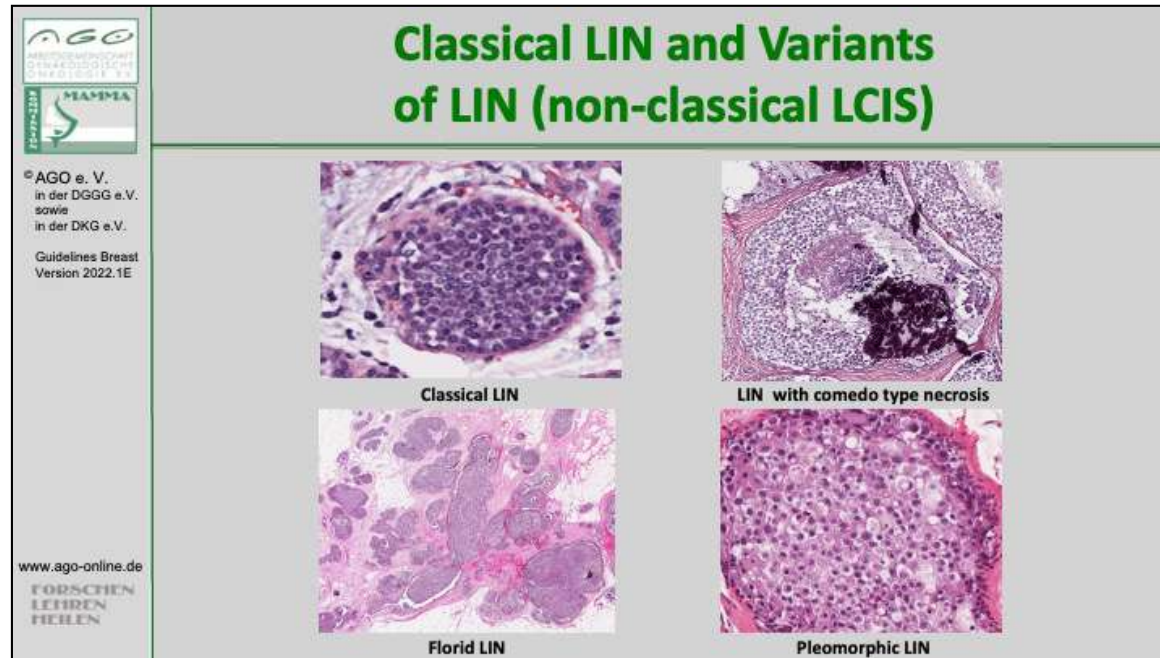
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Statement: Indicator-/ precursor lesion

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## 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

\* Ross DS. Am J Surg Pathol 2011 35: 750–6.

### Statement: Pleomorphic lobular carcinoma in situ (PLCIS)

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## Strategy after Diagnosis of LIN

	Oxford		
	LoE	GR	AGO
<b>LIN in core- / vacuum-assisted biopsy:</b> <ul style="list-style-type: none"> <li>No further measures if LIN (LCIS, classical variant) with involvement of ≤ 3 TDLU (terminal ductulo-lobular unit) in vacuum biopsy and concordant with imaging.</li> <li>Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings.</li> </ul>	2b	C	++
<b>LIN at margins of resection specimen (BCT):</b> <ul style="list-style-type: none"> <li>No further surgery.</li> </ul>	2a	C	++

**Exceptions:**

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

### LIN in core- / vacuum-assisted biopsy (LoE 2b)

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answer yet? *Eur J Surg Oncol*. 2014;40(2):168-175. doi:10.1016/j.ejso.2013.10.024.

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

1. Ciocca R: Presence of lobular carcinoma in situ does not increase recurrence in patients treated with breast-conserving therapy. Ann Surg Oncol 2008; 15:2263-2271



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## 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 yrs., > 1 cm in imaging, ≥ 4 foci.

### General

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Statement: Marker Lesion

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Strategy after Diagnosis of FEA			
	Oxford		
	LoE	GR	AGO
<b>FEA in core biopsy / vacuum-assisted biopsy:</b>			
▪ Open excisional biopsy	2b	B	+
▪ Open excisional biopsy may be omitted under the following circumstances:	2b	B	+
a. a small lesion ( $\leq 2$ TDLU* in vacuum biopsy)			
and			
b. Complete or near complete removal of imaging abnormality			
<b>FEA at margins in resection specimen:</b>			
▪ No further surgery, unless calcifications have not been completely removed	3b	C	++

\* TDLU = Terminal ductal-lobular unit

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## 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) .

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Strategy after Diagnosis of Papilloma			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>■ <b>Papilloma without atypia in core needle or vacuum biopsy:</b> <ul style="list-style-type: none"> <li>→ no further therapy, if biopsy sufficiently representative (100 mm<sup>2</sup>) and concordant with imaging</li> </ul> </li> </ul>	2b	C	+
<ul style="list-style-type: none"> <li>■ <b>Multiple papillomas</b> <ul style="list-style-type: none"> <li>→ open biopsy</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>Papilloma with atypia in core needle or vacuum biopsies:</b> <ul style="list-style-type: none"> <li>→ open biopsy</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>Papilloma at resection margin:</b> <ul style="list-style-type: none"> <li>→ no published data available</li> </ul> </li> </ul>			

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## 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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Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)			
	Oxford		
	LoE	GR	AGO
<b>Radial scar / CSL in core- / vacuum-assisted biopsy:</b>			
→ Open excisional biopsy may be omitted with a small (< 5mm) lesion or complete removal or near complete removal of imaging abnormality	5a	C	+
<b>Radial scar / CSL at margins in resection specimen:</b>			
→ No further surgery	3b	C	++



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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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Rageth CJ, O’Flynn EAM, Pinker K et al.: Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Review, Breast Cancer Res Treat, 2018, doi: 10.1007/s10549-018-05071-1

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Follow-up Imaging for Women Age 50–69 Years with B3-Lesions			
	Oxford		
	LoE	GR	AGO
▪ <b>FEA, non-atypical papilloma</b>			
▪ Screening mammography	5	C	++
▪ <b>LIN</b>			
▪ Mammography (12 months)	3a	C	++
▪ <b>ADH</b>			
▪ Mammography (12 months)	3a	C	++
▪ Women with LIN and ADH should be informed about their elevated risk of breast cancer	3a	C	++

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## Medical Prevention for B3-Lesions With Increased Risk of Associated DCIS or Invasive Carcinoma

		Oxford		
		LoE	GR	AGO
■ Tamoxifen 20 mg for women > 35 years		1a	A	+/-
■ Low-dose Tamoxifen 5 mg (3 years) independent of menopausal status		2b	B	+/-
■ Aromatase inhibitors (Exemestane, Anastrozole) for postmenopausal women		1b	A	+/-
■ Raloxifen for postmenopausal women: Risk reduction of invasive BC only		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)

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