Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
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Lesions of Uncertain Malignant Potential (B3)

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

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

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- **Versions 2005–2019:**
  Albert / Audretsch / Brunnert / Ditsch / Fersis / Friedrich / Friederichs / Gerber / Huober / Kreipe / Nitz / Rody / Schreer / Sinn / Thomssen

- **Version 2020:**
  Fallenberg / Schmidt / Sinn

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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**

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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

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	Oxford		
	LoE	GR	AGO
▪ **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	+

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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.

Strategy after Diagnosis of ADH in Biopsy Sypecimen

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	Oxford LoE	GR	AGO
ADH in core- / vacuum-assisted biopsy:			
▪ Open excisional biopsy	3a	C	++
▪ 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	5a	C	+/-
ADH at margins in open biopsy specimen:			
▪ No further surgery, if incidental finding accompanies invasive or intraductal carcinoma	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

Classical LIN and Variants of LIN (non-classical LCIS)

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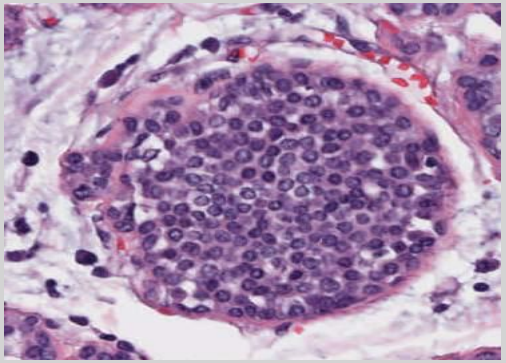
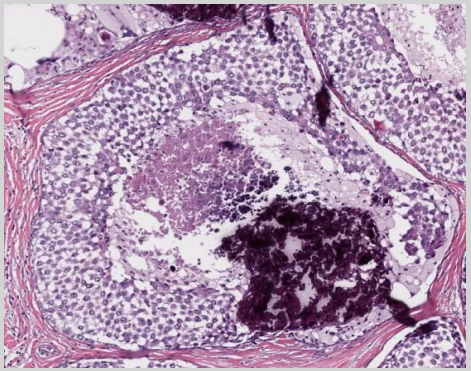
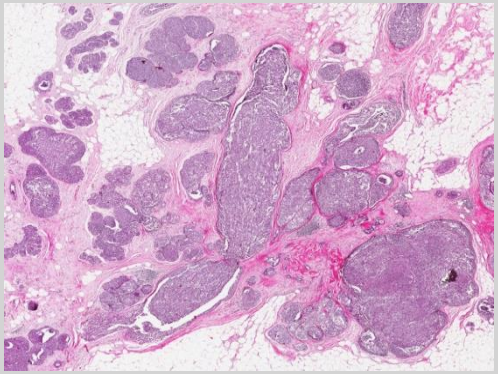


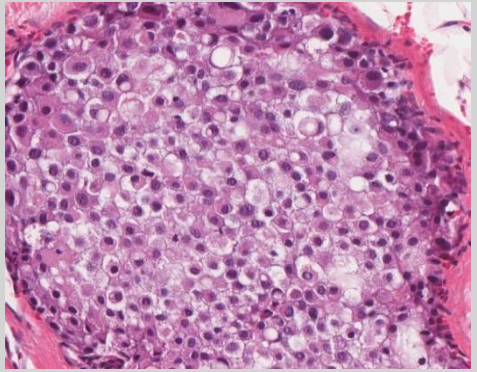
Classical LIN



LIN with comedo type necrosis



Florid LIN



Pleomorphic LIN

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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.**

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Strategy after Diagnosis of LIN

	Oxford LoE	Oxford GR	AGO
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	2b	C	++
▪ Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or if not concordant with imaging findings	2b	C	++
LIN at margins of resection specimen (BCT):			
▪ No further surgery	2a	C	++

Exceptions:

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

a) Imaging abnormality is not removed

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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 > = 57J, > 1 cm in imaging, > = 4 foci.

Strategy after Diagnosis of FEA

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	Oxford LoE	Oxford GR	AGO
FEA in core biopsy/vacuum-assisted biopsy:			
Open excisional biopsy may be omitted under the following circumstances:	3b	C	+
a. a small lesion (≤ 2 TDLU* in vacuum biopsy) and			
b. Complete or near complete removal of imaging abnormality			
Representative open excisional biopsy in radiologically extensive microcalcifications or discordance to the radiological result	5	C	+
FEA at margins in resection specimen:			
No further surgery, unless calcifications have not been completely removed	3b	C	++

* 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
▪ **Papilloma without atypia in core needle or vacuum biopsy:**			
→ **no further therapy, if biopsy sufficiently representative (100 mm²) and concordant with imaging**	3a	C	++
▪ **Multiple papillomas**			
→ **open biopsy**	3a	C	++
▪ **Papilloma with atypia in core needle or vacuum biopsies:**			
→ **open biopsy**	3a	C	++
▪ **Papilloma at resection margin:**			
→ **no published data available**			

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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%**

Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL)

	Oxford LoE	Oxford GR	AGO
▪ **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	5a	C	+
▪ **Radial scar / CSL at margins in resection specimen:**			
→ 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.

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

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

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	Oxford		
	LoE	GR	AGO
FEA, non-atypical papilloma			
▪ Screening mammography	5	C	++
LIN			
▪ Mammography (12 months)	3a	C	++
ADH			
▪ Mammography (12 months)	3a	C	++
▪ Women with LIN and ADH should be informed about their elevated risk of breast cancer	3a	C	++

Medical Prevention for Lesions with Uncertain Biological Behavior (incl. LIN, ADH)

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

Tamoxifen Chemoprevention—End of the Road?

	Placebo	Verum
Participants	18.322	18.355
Invasive breast cancer	805	537
ER-positive	632	350
ER-negative	144	173
Breast cancer-related death	48	60

Narod. JAMA Oncol 1:1033-4, 2015

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