Guidelines Breast
Version 2024.1E

Lesions of Uncertain Malignant Potential (B3)

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

Lesions of Uncertain Malignant Potential (B3)

Guidelines Breast
Version 2024.1E

Versionen 2005–2023:

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

Version 2024:

Friedrich / Sinn

Pathology Reporting for Minimal Invasive Biopsies

Guidelines Breast
Version 2024.1E

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**

Guidelines Breast
Version 2024.1D

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, nipple adenoma, microglandular adenosis, mucocele-like lesion, nodular fasciitis, desmoid-type fibromatosis, spindle cell lesion of unknown significance

Guidelines Breast
Version 2024.1E

Management after Minimally Invasive Biopsy

	Oxford		
	LoE	GR	AGO
▪ **Interdisciplinary conference: Concordant findings in pathology and imaging?**			
▪ yes: proceed according to histologic type and dimension of lesion	3a	C	++
▪ no: open biopsy	3a	C	++
Vacuum-assisted biopsy (after core biopsy)	5	D	+

Guidelines Breast
Version 2024.1E

Strategy after Diagnosis of ADH in Biopsy Sypecimen

	Oxford		
	LoE	GR	AGO
ADH in core- / vacuum-assisted biopsy:			
▪ **Open excisional biopsy**	3a	C	++
▪ **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	5	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

Guidelines Breast
Version 2024.1E

Lobular Intraepithelial Neoplasia (LIN / LCIS)

- 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 lesions with elevated risk → potentially **B5a**
- Indicator / precursor lesion:
  Ipsi- and contralaterally increased breast cancer risk:
  7x after 10 years

Guidelines Breast
Version 2024.1E

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 lobular neoplasia (C-LCIS)	4 - 16%	[1-3]
Non-classical lobular neoplasia (pleomorphic, florid LCIS, NC-LCIS)	33 - 39%	[3, 4]
Atypical ductal hyperplasia (ADH)	23%	[1]
Flat epithelial atypia (FEA)	0 - 14%	[5, 6]
Papilloma	12%	[7]
- no atypia	6 - 10%	[7, 8]
- atypia	21 -29%	[8, 9]
Radial scar or complex sclerosing lesion	7 - 11%	[10-12]
- no atypia	5%	[12]
- atypia	25%	[13]

Risk of malignant disease during follow-up*

Guidelines Breast
Version 2024.1E

* i.e. ipsilateral or contralateral disease irrespective of localization of prior lesion

Risk lesion	**Upgrade rate to in situ or invasive Ca**
LIN/LCIS	7x / 10 yrs (ipsi-/contralateral)
Atypical ductal hyperplasia (ADH)	3-5x / 10 years (ipsi-/contralateral)
Papilloma	
• no atypia	4.6% (ipsilateral)
• atypia	13% (ipsilateral)

Guidelines Breast
Version 2024.1E

LCIS with elevated risk

- **Non-classical LCIS:**
  - **Pleomorphic LCIS: high-grade cellular atypia, common involvement of ducts with comedo necrosis and microcalcifications**
  - **Florid LCIS: involvement of multiple lobuli with a maximum extension until confluence and involvement of ductuli and neighboring TDLU**
- **Microinvasion in classical and non-classical LCIS*:**
  - **classical LCIS: n = 11**
  - **florid LCIS: n = 4**
  - **pleomorphic LCIS: n = 1**

Microinvasion in 0.37% of all LCIS (n = 4310) and in 0.43% among all invasive lobular breast cancers (n = 3740).

* **Ross DS & Hoda SA. Am J Surg Pathol 2011; 35: 750–6.**

Guidelines Breast
Version 2024.1E

Strategy after Diagnosis of LIN / LCIS

	Oxford		
	LoE	GR	AGO
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.	2b	C	++
▪ Open excisional biopsy, with pleomorphic LIN, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings.	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

	Oxford LoE	Oxford GR	Oxford AGO
FEA in core biopsy / vacuum-assisted biopsy:			
Open excisional biopsy	2b	B	+
Open excisional biopsy may be omitted under the following circumstances: 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:			
No further surgery, unless calcifications have not been completely removed	3b	C	++

* TDLU = Terminal ductal-lobular unit

Guidelines Breast
Version 2024.1E

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) .

Guidelines Breast
Version 2024.1E

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 (100mm3) and concordant with imaging**	2b	C	+
▪ **Multiple papillomas (>2 mm)**			
→ **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**			

Guidelines Breast
Version 2024.1E

Radially Sclerosing Lesion

- **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)

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ **Radial scar / CSL in core- / vacuum-assisted biopsy:**			
▪ **Open excisional biopsy**	3a	C	+
▪ **Without atypia**	3a	C	+
▪ **With atypia**	3a	C	++
→ **Omission of open excisional biopsy if small (< 5mm) lesion or (near) complete removal of imaging abnormality**	5	C	+
▪ **Radial scar / CSL at margins in resection specimen:**			
→ **No further surgery**	3b	C	++

Guidelines Breast
Version 2024.1E

Breast Cancer Early Detection: Follow-up Imaging for Women Age 50–69 Years with B3-Lesions

	Oxford		
	LoE	GR	AGO
▪ **FEA, non-atypical papilloma, radial sclerosing lesion**			
▪ Screening mammography	5	C	++
▪ **LIN / LCIS**			
▪ 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 Patients with Increased Risk of DCIS or Invasive Carcinoma

Guidelines Breast
Version 2024.1E

	Oxford		
	LoE	GR	AGO
▪ 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

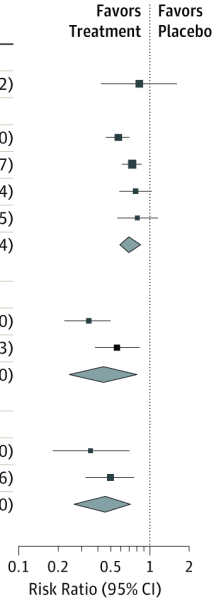
** Risk situation as defined in NSABP P1-trial (1.66% in 5 years)

Medical endocrine Prevention

Guidelines Breast
Version 2024.1D

Risk Reduction of Invasive Breast Cancer: Meta-analysis of Primary Prevention Trials

Source	Trial	Mean, y: Intended Treatment Duration	Mean, y: Total Follow-up	No. With Invasive Breast Cancer/Total Participants (%): Treatment	No. With Invasive Breast Cancer/Total Participants (%): Placebo	Rate per 1000 Women-Years: Treatment	Rate per 1000 Women-Years: Placebo	Risk Ratio (95% CI)
Tamoxifen, low dose								
DeCensi et al,[41] 2013	HOT	5	6.2	18/938 (1.9)	22/946 (2.3)	3.13	3.78	0.83 (0.42-1.62)
Tamoxifen								
Fisher et al,[82] 2005	NSABP-1	5	6.1	145/6681 (2.2)	250/6707 (3.7)	3.59	6.29	0.57 (0.46-0.70)
Cuzick et al,[74] 2015	IBIS-I	5	16.0	214/3579 (6.0)	289/3575 (8.1)	3.86	5.29	0.73 (0.61-0.87)
Powles et al,[83] 2007	Marsden	5	13.2	82/1238 (6.6)	104/1233 (8.4)	4.80	6.10	0.78 (0.58-1.04)
Veronesi et al,[84] 2007	Italian	4[a]	11.2	53/2700 (2.0)	66/2708 (2.4)	1.77	2.21	0.80 (0.56-1.15)
Combined I^2 = 38.7%; Q = 4.9 for heterogeneity; P = .18								0.69 (0.59-0.84)
Raloxifene								
Martino et al,[45] 2004	MORE/CORE	4 or 8[b]	5.4[b]	40/5129 (0.8)	58/2576 (2.3)	1.40	4.20	0.34 (0.22-0.50)
Barrett-Connor et al,[48] 2006	RUTH	5.1[a]	5.6	40/5044 (0.8)	70/5057 (1.4)	1.43	2.49	0.56 (0.38-0.83)
Combined I^2 = 66.4%; Q = 3.0 for heterogeneity; P = .08								0.44 (0.24-0.80)
Aromatase inhibitor								
Goss et al,[44] 2011	MAP.3	5[c]	2.9	11/2285 (0.5)	32/2275 (1.4)	1.66	4.85	0.35 (0.18-0.70)
Cuzick et al,[4] 2014	IBIS-II	5	5	32/1920 (1.7)	64/1944 (3.3)	3.29	6.62	0.50 (0.32-0.76)
Combined I^2 = 0.0%; Q = 0.8 for heterogeneity; P = .39								0.45 (0.26-0.70)



Nelson et al. JAMA. 2019;322(9):868-886. doi:10.1001/jama.2019.5780