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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)

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)

(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

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/>
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4. Rageth CJ, O'Flynn EAM, Pinker K, Kubik-Huch RA, Munding A, Decker T, et al. Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast Cancer Res Treat. 2019 Apr;174(2):279–96.
5. Scottish Intercollegiate Guidelines Network (SIGN) (2013) SIGN 134 • Treatment of primary breast cancer. <http://www.sign.ac.uk/pdf/SIGN134.pdf>
6. World Health Organization: WHO Classification of Tumours of the Breast. Lokuhetty D, White VA, Watanabe R, Cree IA (Hrsg.) 2019.


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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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.
3. Wells C (ed.) (2006) Quality assurance guidelines for pathology: Cytological and histological non-operative procedures. In: European guidelines for quality assurance in breast cancer screening and diagnosis. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, Koch von F, editors. Luxembourg: Office for Official Publications of the European Communities, ISBN 92-79-01258-4 pp. 221-256 Retrieved from <http://www.euref.org/european-guidelines>
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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

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/>
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3. 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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10. World Health Organization: WHO Classification of Tumours of the Breast. Lokuhetty D, White VA, Watanabe R, Cree IA (Hrsg.) 2019.


Management after Minimally Invasive Biopsy

	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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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/>
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5. Houssami N et al: Borderline breast core needle histology: predictive values for malignancy in lesions of uncertain malignant potential (B3). *Br J Cancer* 2007; 96:1253-1257
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8. Neal L, Sandhu NP, Hieken TJ et al.: Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on

core needle biopsy. Mayo Clin Proc. 2014 Apr;89(4):536-47

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10. Saladin C, Haueisen H, Kampmann G et al. Lesions with unclear malignant potential (B3) after minimally invasive breast biopsy: evaluation of vacuum biopsies performed in Switzerland and recommended further management. Acta Radiol. 2016 Jul;57(7):815–21.
11. Sinn HP, Flechtenmacher C, Aulmann S. Diagnostik benigner duktaler Epithelproliferationen der Mamma in der Stanzbiopsie. Der Pathologe. Springer Berlin Heidelberg; 2014 Feb;35(1):18–25.
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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.

1. Calhoun BC, Collins LC. Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. *Histopathology*. 2016;68(1):138-151. doi:10.1111/his.12852.
2. Co M, Kwong A, Shek T. Factors affecting the under-diagnosis of atypical ductal hyperplasia diagnosed by core needle biopsies - A 10-year retrospective study and review of the literature. *Int J Surg*. 2018;49:27-31. doi:10.1016/j.ijsu.2017.11.005.
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21. doi:10.1001/jamaoncol.2016.3136.
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11. Sinn HP, Flechtenmacher C, Aulmann S. Diagnostik benigner duktaler Epithelproliferationen der Mamma in der Stanzbiopsie. *Der Pathologe.* 2014;35(1):18-25. doi:10.1007/s00292-013-1886-7.


Strategy after Diagnosis of ADH in Biopsy Specimen

	Oxford		
	LoE	GR	AGO
ADH in core- / vacuum-assisted biopsy:			
▪ Open excisional biopsy	3a	C	++
▪ Open excisional biopsy may be omitted, if:	5a	C	+/-
a) No mass-lesion radiologically, and			
b) a small lesion (≤ 2 TDLU*) in vacuum biopsy, and			
c) complete removal of imaging abnormality			
ADH at margins in open biopsy specimen:			
▪ No further surgery, if incidental finding accompanies invasive or intraductal carcinoma	3a	C	++

* Terminal ductal-lobular unit

- Allison, K. H., Rendi, M. H. et al. (2016). Histological features associated with diagnostic agreement in atypical ductal hyperplasia of the breast: illustrative cases from the B-Path study. *Histopathology*, 69(6), 1028–1046. <http://doi.org/10.1111/his.13035>
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- Hayes B et al: Correlation of needle core biopsy with excision histology in screen-detected B3 lesions: the Merrion Breast Screening Unit experience. *J Clin Pathol* 2009; 62:1136-1140.
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- Menes TS, Rosenberg R, Balch S et al.: Upgrade of high-risk breast lesions detected on mammography in the Breast Cancer Surveillance Consortium. *Am J Surg*. 2014 Jan;207(1):24-31.

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13. Yu, C.-C., Ueng, S.-H., Cheung, Y.-C. et al. (2015). Predictors of Underestimation of Malignancy after Image-Guided Core Needle Biopsy Diagnosis of Flat Epithelial Atypia or Atypical Ductal Hyperplasia. *The Breast Journal*, 21(3), 224–232. <http://doi.org/10.1111/tbj.12389>



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Lobular Intraepithelial Neoplasia (LIN)

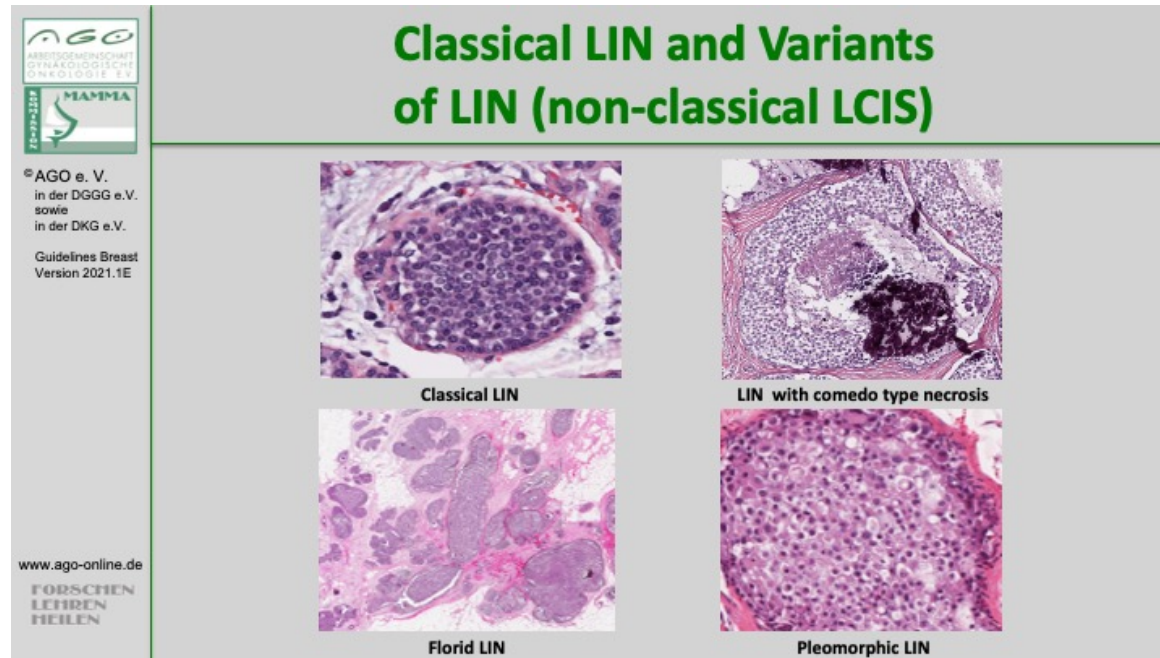
- Includes:
 - Atypical lobular hyperplasia
 - Classical lobular carcinoma in situ (LIN, classical variant)
 - Non-Classical lobular carcinoma in situ (LIN, classical variant)
- LIN 1–3 classification is not sufficiently validated prognostically
- Non-Classical LIN (pleomorphic LIN, florid LIN) are classified 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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2. Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. *J Clin Oncol*. 2005 Aug 20;23(24):5534–41.
3. Nakhliis F, Gilmore L, Gelman R et al. Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In-situ in Patients with Lobular Neoplasia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 020). *Ann Surg Oncol*. Springer International Publishing; 2016 Mar;23(3):722–8.



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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)

1. Nakhli F, Harrison BT, Giess CS, et al. Evaluating the Rate of Upgrade to Invasive Breast Cancer and/or Ductal Carcinoma In Situ Following a Core Biopsy Diagnosis of Non-classic Lobular Carcinoma In Situ. *Ann Surg Oncol*. 2019;26(1):55-61. doi:10.1245/s10434-018-6937-0.
2. Desai AA, Jimenez RE, Hoskin TL, Day CN, Boughhey JC, Hieken TJ. Treatment Outcomes for Pleomorphic Lobular Carcinoma In Situ of the Breast. *Ann Surg Oncol*. 2018;25(10):3064-3068. doi:10.1245/s10434-018-6591-6.
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Statement: Lobular carcinoma in situ with microinvasion

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Strategy after Diagnosis of LIN

	Oxford		
	LoE	GR	AGO
LIN in core- / vacuum-assisted biopsy: <ul style="list-style-type: none"> 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, florid LIN (LIN 3), or LIN with comedo type necrosis or if not concordant with imaging findings 	2b	C	++
LIN at margins of resection specimen (BCT): <ul style="list-style-type: none"> No further surgery 	2a	C	++
Exceptions:			
a) Pleomorphic LIN, florid LIN, or LIN with necrosis			
a) Imaging abnormality is not removed			

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


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

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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.

General

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Statement: Marker Lesion

1. Lamb LR, Bahl M, Gadd MA, Lehman CD. Flat Epithelial Atypia: Upgrade Rates and Risk-Stratification Approach to Support Informed Decision Making. *J Am Coll Surg*. 2017;225(6):696-701. doi:10.1016/j.jamcollsurg.2017.08.022.
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Strategy after Diagnosis of FEA

	Oxford		
	LoE	GR	AGO
FEA in core biopsy/vacuum-assisted biopsy: ▪ 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 ▪ Representative open excisional biopsy in radiologically extensive microcalcifications or discordance to the radiological result	3b	C	+
FEA at margins in resection specimen: ▪ 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
Papilloma without atypia in core needle or vacuum biopsy: → no further therapy, if biopsy sufficiently representative (100 mm ²) 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 radial 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
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

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

	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	++

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

	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**

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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

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