Guidelines Breast
Version 2023.1D

FORSCHEN
LEHREN
HEILEN

Läsionen mit unsicherem biologischen Potenzial (B3)

(ADH, LIN, FEA, Papillom, Radiäre Narbe/komplexe sklerosierende Läsion)

Läsionen mit unklarem biologischen Potenzial (B3)

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

- **Version 2023:**
  Kolberg-Liedtke / Reimer / Sinn

<u>Pubmed 2010-2022 queries</u>

Lobular neoplasia (169 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] : "2023/01/01"[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 (101 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] : "2023/01/01"[dp]) AND ("atypical ductal hyperplasia"[ti] OR "atypical hyperplasia"[ti] OR "ADH"[ti]) AND ("english"[la] OR "german"[la])

Flat epithelial atypia (59 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] : "2023/01/01"[dp]) AND ("flat epithelial atypia"[ti] OR "columnar cell"[ti] OR "FEA"[ti]) AND ("english"[la] OR "german"[la])

Papilloma (278 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] : "2023/01/01"[dp]) AND ("papilloma"[ti] OR "papillary"[ti]) AND ("english"[la] OR "german"[la]) NOT virus[ti]

Radial scar (25 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] : "2023/01/01"[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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Pathologische Berichterstellung für minimalinvasive Biopsien

B-Klassifikation*

B1 = Normalgewebe oder nicht verwertbares Material
B2 = Benigne Läsion
B3 = Benigne Läsionen mit unsicherem biologischen Potenzial
B4 = Malignitätsverdächtig
B5 = Malignom
B5a: In-situ-Karzinom
B5b: Invasives Karzinom
B5c: Nicht zu entscheiden, ob invasiv oder in situ
B5d: Malignom anderer Histogenese oder Metastase

* **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**

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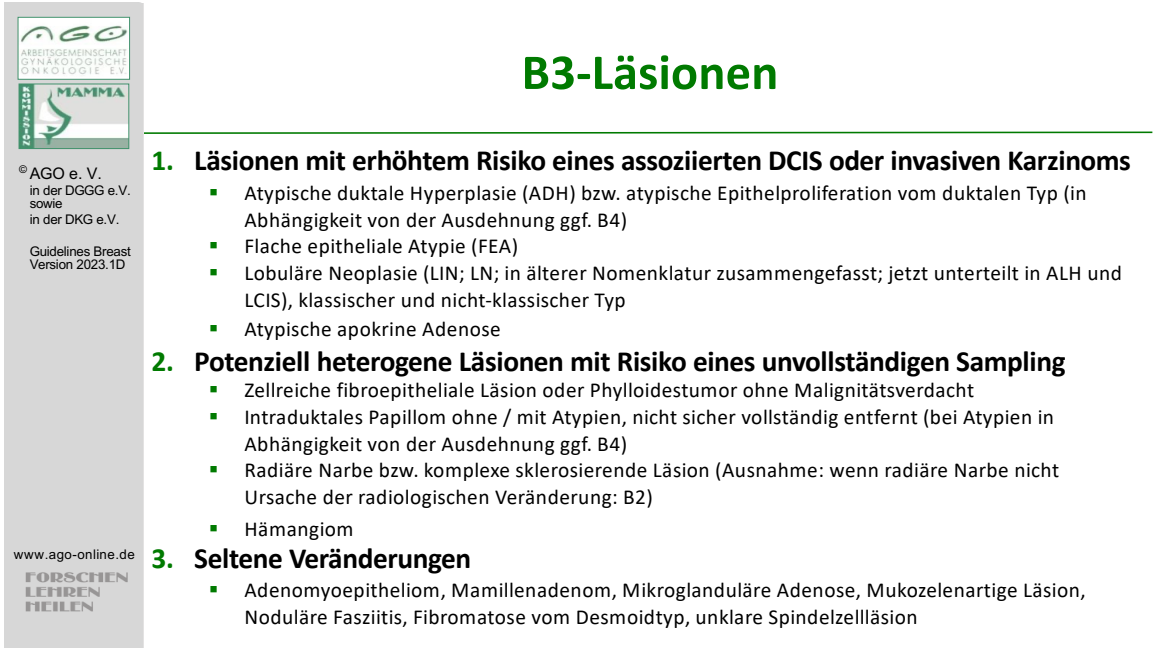

B3-Läsionen

1. **Läsionen mit erhöhtem Risiko eines assoziierten DCIS oder invasiven Karzinoms**
   - Atypische duktale Hyperplasie (ADH) bzw. atypische Epithelproliferation vom duktalen Typ (in Abhängigkeit von der Ausdehnung ggf. B4)
   - Flache epitheliale Atypie (FEA)
   - Lobuläre Neoplasie (LIN; LN; in älterer Nomenklatur zusammengefasst; jetzt unterteilt in ALH und LCIS), klassischer und nicht-klassischer Typ
   - Atypische apokrine Adenose
2. **Potenziell heterogene Läsionen mit Risiko eines unvollständigen Sampling**
   - Zellreiche fibroepitheliale Läsion oder Phylloidestumor ohne Malignitätsverdacht
   - Intraduktales Papillom ohne / mit Atypien, nicht sicher vollständig entfernt (bei Atypien in Abhängigkeit von der Ausdehnung ggf. B4)
   - Radiäre Narbe bzw. komplexe sklerosierende Läsion (Ausnahme: wenn radiäre Narbe nicht Ursache der radiologischen Veränderung: B2)
   - Hämangiom
3. **Seltene Veränderungen**
   - Adenomyoepitheliom, Mamillenadenom, Mikroglanduläre Adenose, Mukozelenartige Läsion, Noduläre Fasziitis, Fibromatose vom Desmoidtyp, unklare Spindelzelläsion

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Management nach minimalinvasiver Biopsie

	Oxford LoE	Oxford GR	Oxford AGO
Interdisziplinäre Konferenz: Pathologie und Bildgebung konkordant?			
ja: Vorgehen gemäß histologischem Typ und Ausdehnung des Befundes	3a	C	++
nein: offene PE	3a	C	++
Vakuumbiopsie (nach Stanzbiopsie)	5	D	+

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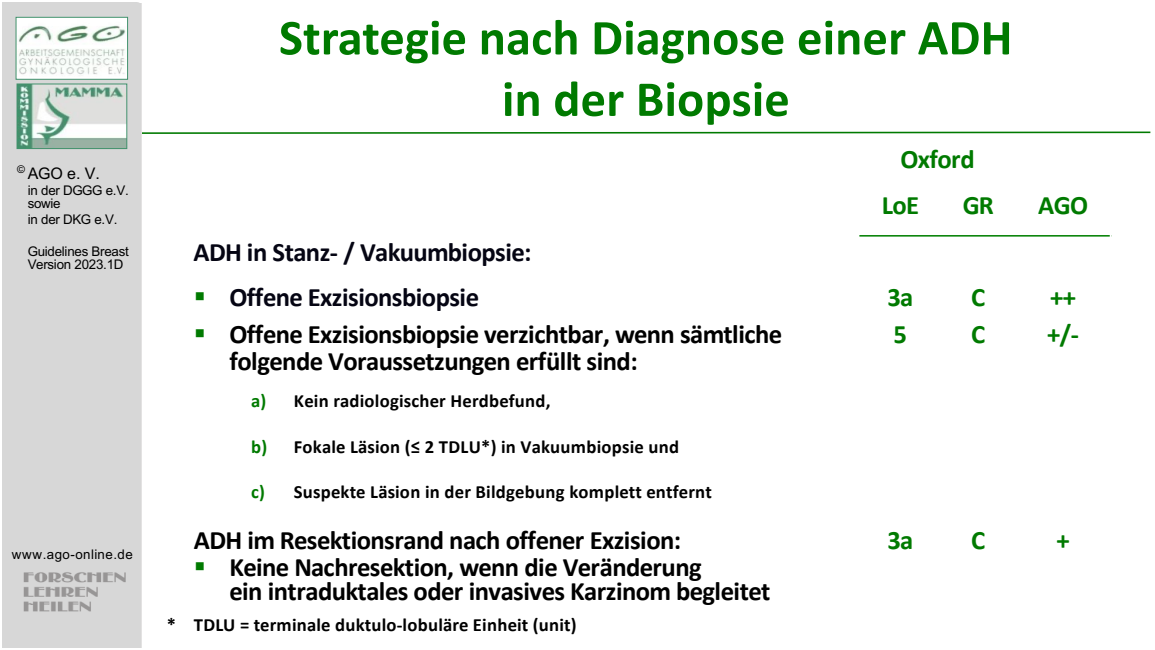

Strategie nach Diagnose einer ADH in der Biopsie

	Oxford		
	LoE	GR	AGO
ADH in Stanz- / Vakuumbiopsie:			
▪ **Offene Exzisionsbiopsie**	3a	C	++
▪ **Offene Exzisionsbiopsie verzichtbar, wenn sämtliche folgende Voraussetzungen erfüllt sind:**	5	C	+/-
a) Kein radiologischer Herdbefund,			
b) Fokale Läsion (≤ 2 TDLU*) in Vakuumbiopsie und			
c) Suspekte Läsion in der Bildgebung komplett entfernt			
ADH im Resektionsrand nach offener Exzision:	3a	C	+
▪ **Keine Nachresektion, wenn die Veränderung ein intraduktales oder invasives Karzinom begleitet**			

* TDLU = terminale duktulo-lobuläre Einheit (unit)

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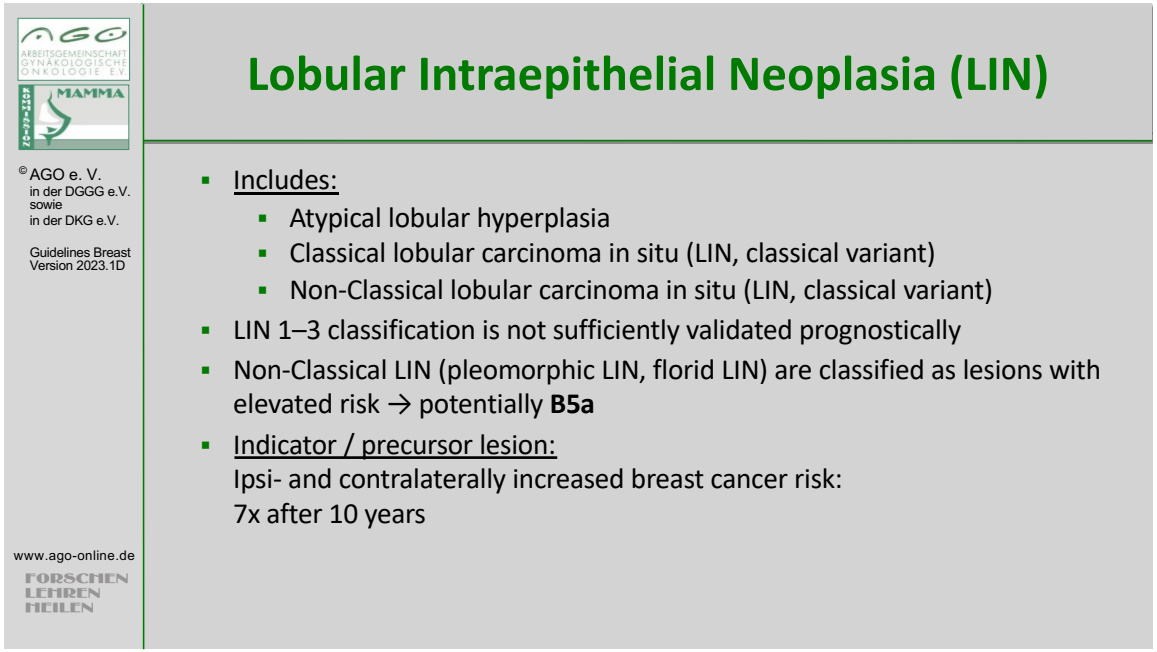

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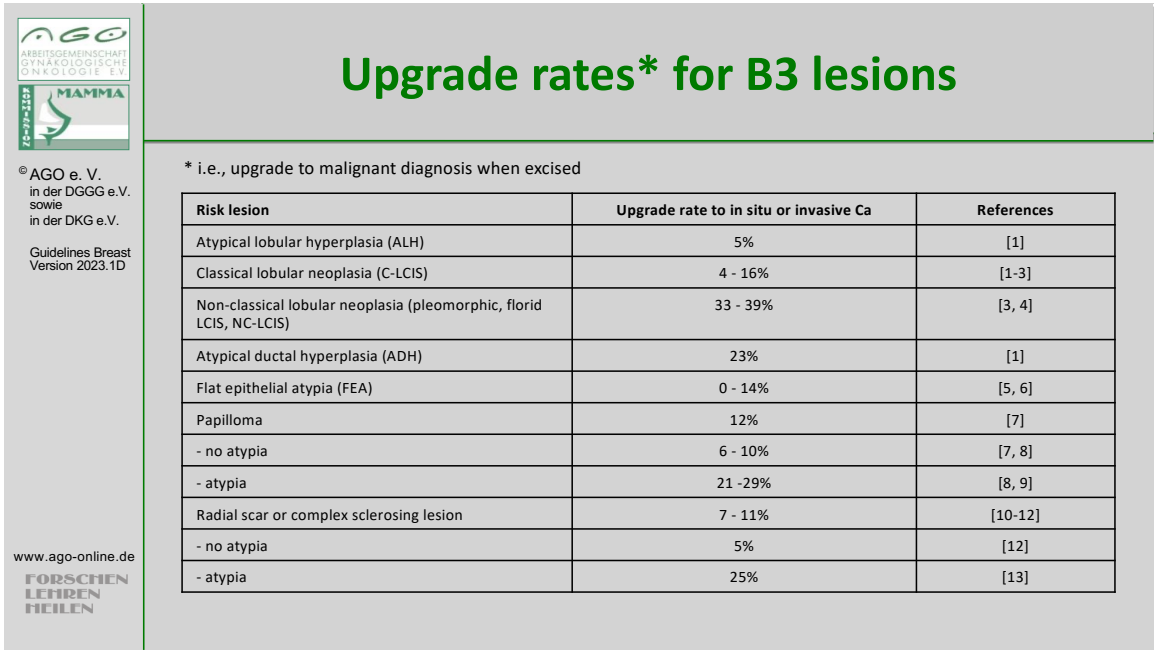

Upgrade rates* for B3 lesions

* 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]

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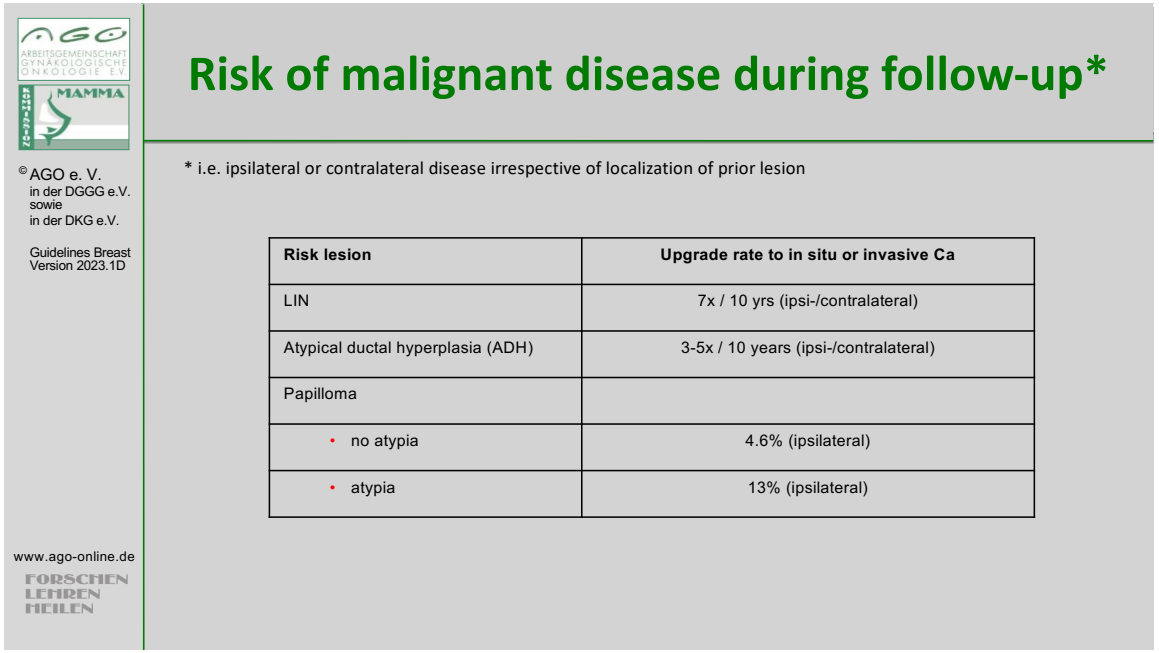

Allgemeines

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Papillome

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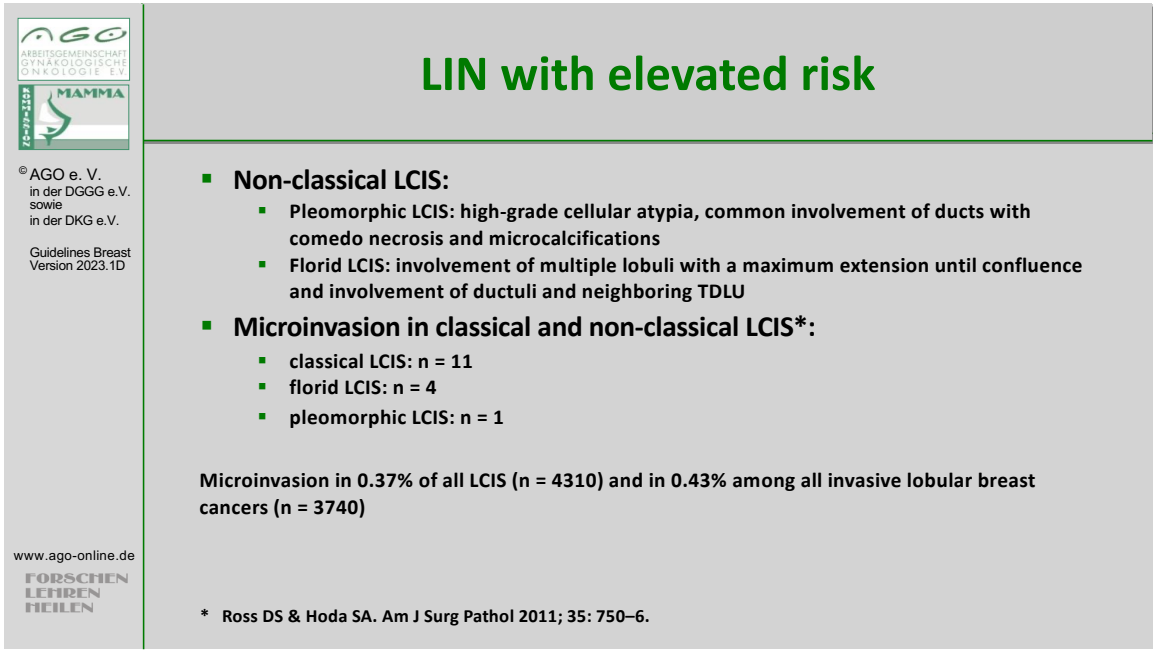

Statement: Pleomorphic lobular carcinoma in situ (PLCIS)

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Statement: Florid lobular carcinoma in situ (FLCIS)

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7. Nakhlis, F. *et al.* Presence of Non-classic LCIS Is Not a Contraindication to Breast Conservation in Patients with Concomitant Invasive Breast Cancer or DCIS. *Ann Surg Oncol* **29**, 7696–7702 (2022).

Statement: Lobular carcinoma in situ with microinvasion

1. Nemoto, T., Castillo, N., Tsukada, Y et al. (1998). Lobular carcinoma in situ with microinvasion. Journal of Surgical Oncology, 67(1), 41–46.
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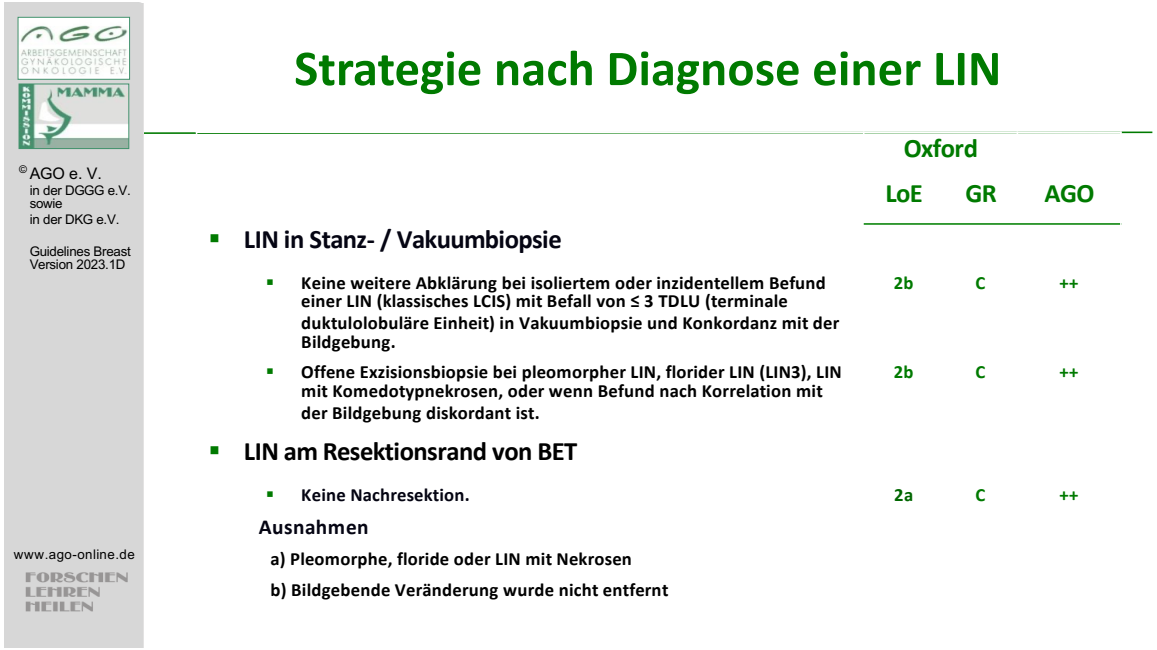

Strategie nach Diagnose einer LIN

	Oxford LoE	Oxford GR	AGO
LIN in Stanz- / Vakuumbiopsie			
Keine weitere Abklärung bei isoliertem oder inzidentellem Befund einer LIN (klassisches LCIS) mit Befall von ≤ 3 TDLU (terminale duktulolobuläre Einheit) in Vakuumbiopsie und Konkordanz mit der Bildgebung.	2b	C	++
Offene Exzisionsbiopsie bei pleomorpher LIN, florider LIN (LIN3), LIN mit Komedotypnekrosen, oder wenn Befund nach Korrelation mit der Bildgebung diskordant ist.	2b	C	++
LIN am Resektionsrand von BET			
Keine Nachresektion.	2a	C	++

Ausnahmen

a) Pleomorphe, floride oder LIN mit Nekrosen

b) Bildgebende Veränderung wurde nicht entfernt

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

1. Kunjummen, J., Rodriguez, K., Newell, M. S., Hanley, K. & Cohen, M. A. Management of Lobular Neoplasia Found on Core Needle Biopsy Performed for Calcifications Using Precise Radiologic-Pathologic Correlation. *Am J Roentgenol* **216**, 1476–1485 (2021).
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6. Taylor, L. J. *et al.* Surgical Management of Lobular Carcinoma In Situ: Analysis of the National Cancer Database. *Annals of Surgical Oncology* **25**, 2229–2234 (2018).
7. Khoury, M. E. *et al.* Is the outcome at surgery different when flat epithelial atypia and lobular neoplasia are found in association at biopsy? *Br J Radiology* **90**, 20160750 (2017).
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Management Recommendations. *Annals of Surgical Oncology* **24**, 2848–2854 (2017).
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12. Calhoun, B. C. *et al.* Lobular neoplasia diagnosed on breast Core biopsy: frequency of carcinoma on excision and implications for management. *Annals of diagnostic pathology* **25**, 20–25 (2016).
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14. Calhoun, B. C. & Collins, L. C. Recommendations for excision following core needle biopsy of the breast: a contemporary evaluation of the literature. *Histopathology* **68**, 138–151 (2016).

<u>LIN accompanying intraductal or invasive carcinoma in patients with BCT (LoE 2a</u>)
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

Strategie nach Diagnose einer FEA

	Oxford LoE	Oxford GR	Oxford AGO
FEA in Stanz- / Vakuumbiopsie:			
Offene Exzisionsbiopsie	2b	B	+
Auf offene Biopsie kann verzichtet werden unter folgenden Voraussetzungen:	2b	B	+
a. Kleinherdiger Befund (≤ 2 TDLU* in Vakuumbiopsie) und			
b. Entfernung oder weitgehend vollständige Entfernung der auffälligen Läsion in der Bildgebung (≥ 90 %)			
FEA im Resektionsrand nach Exzisionsbiopsie:			
Keine Nachresektion, außer bei verbliebenem mammographischem Korrelat	3b	C	++

* TDLU = terminale duktulolobuläre Einheit

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2. Acott, A. A. & Mancino, A. T. Flat epithelial atypia on core needle biopsy, must we surgically excise? *Am J Surg* **212**, 1211–1213 (2016).
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4. Samples, L. S. *et al.* Surgical implications and variability in the use of the flat epithelial atypia diagnosis on breast biopsy specimens. *Breast* **34**, 34–43 (2017).
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7. Schiaffino, S. *et al.* Flat epithelial atypia: conservative management of patients without residual microcalcifications post-vacuum-assisted breast biopsy. *Br J Radiology* **91**, 20170484 (2018).
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11. Liu, C. *et al.* Pure flat epithelial atypia identified on core needle biopsy does not require excision. *Eur J Surg Oncol* **46**, 235–239 (2020).
12. Srour, M. K. *et al.* Flat epithelial atypia on core needle biopsy does not always mandate excisional biopsy. *Breast J* **26**, 679–684 (2020).
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14. Wahab, R. A., Lee, S.-J., Mulligan, M. E., Zhang, B. & Mahoney, M. C. Upgrade Rate of Pure Flat Epithelial Atypia Diagnosed at Core Needle Biopsy: A Systematic Review and Meta-Analysis. *Radiology Imaging Cancer* **3**, e200116 (2021).
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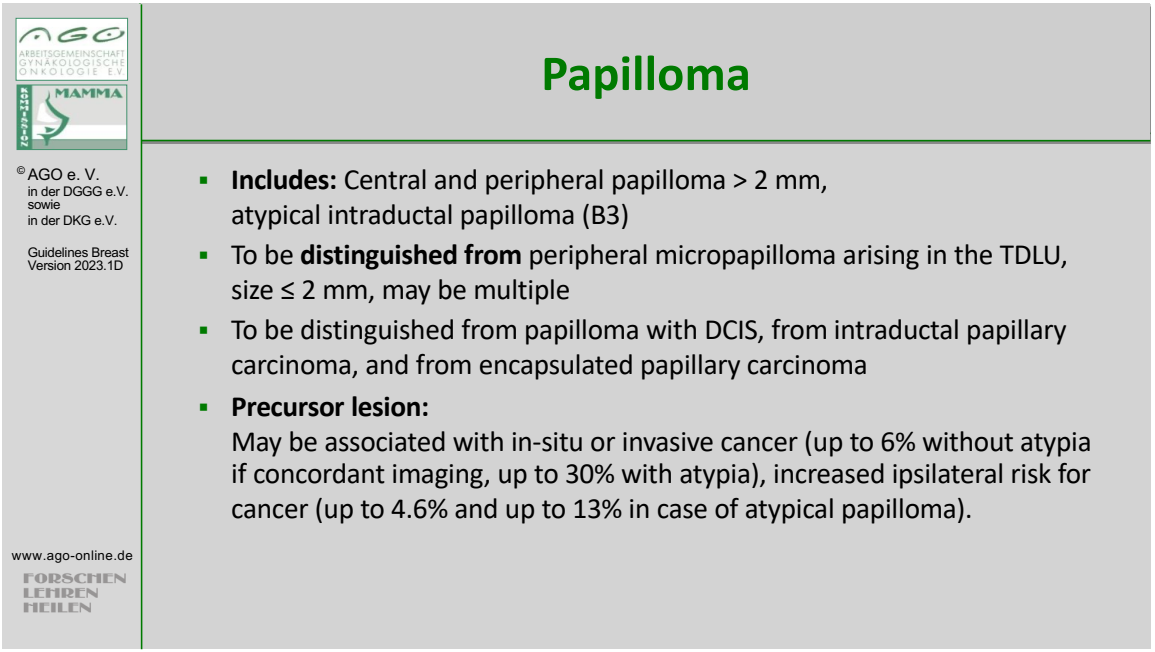

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Vorgehen nach Diagnose eines Papilloms

	Oxford		
	LoE	GR	AGO
▪ **Solitäres Papillom ohne Atypien in Stanz- / Vakuumbiopsie**			
▪ **Keine weiteren Maßnahmen, wenn Biopsie ausreichend repräsentativ (100 mm²) und keine Diskordanz zur Bildgebung**	2b	C	+
▪ **Multiple Papillome (> 2 mm)**			
▪ **Offene Biopsie**	3a	C	++
▪ **Atypisches Papillom in Stanz- / Vakuumbiopsie**			
▪ **Offene Biopsie**	3a	C	++
▪ **Papillom am Rand von Resektaten**			
▪ **Keine verfügbaren Daten**			

1. Jee, Y. *et al.* Intraductal Papilloma on Breast Biopsy: Upstaging Rate and Implications for Practice Guidelines. *Am Surg***88**, 1467–1470 (2022).
2. Corbin, H. *et al.* Upgrade rates of intraductal papilloma with and without atypia diagnosed on core needle biopsy and clinicopathologic predictors. *Hum Pathol* **128**, 90–100 (2022).
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8. Genco, I. S., Tugertimur, B., Manolas, P. A., Hasanovic, A. & Hajiyeva, S. Upgrade rate of intraductal papilloma without atypia on breast core needle biopsy: A clinical, radiological and pathological correlation study. *Am J Surg* **220**, 677–681 (2020).
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11. Qiu, L. *et al.* Diagnosis of Papillary Breast Lesions on Core Needle Biopsy: Upgrade Rates and Interobserver Variability. *Int J Surg Pathol* **27**, 736–743 (2019).
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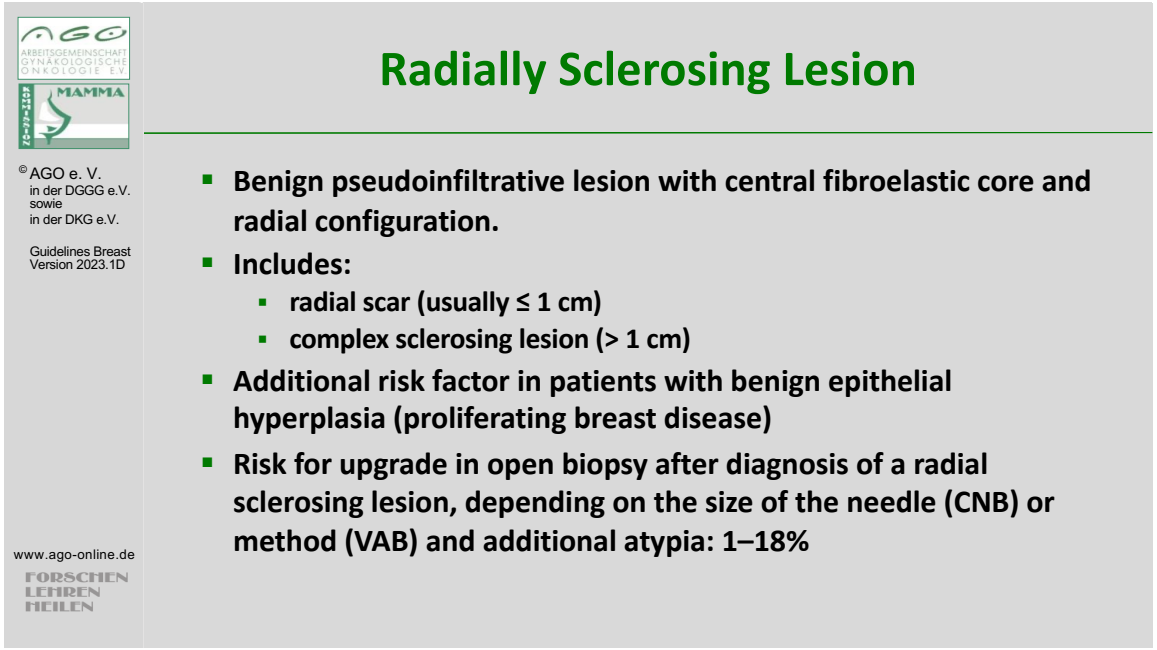
13. Liu, C. *et al.* Risk of malignancy in papillary neoplasms of the breast. *Breast Cancer Res Tr* **178**, 87–94 (2019).
14. Kiran, S. *et al.* Are we overtreating intraductal papillomas? *The Journal of surgical research* **231**, 387–394 (2018).



1. Donaldson, A. R., Sieck, L., Booth, C. N. & Calhoun, B. C. Radial scars diagnosed on breast core biopsy: Frequency of atypia and carcinoma on excision and implications for management. *Breast (Edinburgh, Scotland)* **30**, 201–207 (2016).
2. Leong, R. Y., Kohli, M. K., Zeizafoun, N., Liang, A. & Tartter, P. I. Radial Scar at Percutaneous Breast Biopsy That Does Not Require Surgery. *Journal of the American College of Surgeons* **223**, 712–716 (2016).
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10. Rakha, E. *et al.* Outcome of radial scar/complex sclerosing lesion associated with epithelial proliferations with atypia diagnosed on breast core biopsy: results from a multicentric UK-based study. *J Clin Pathol* **72**, 800 (2019).
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16. Trombadori, C. M. L. *et al.* Radial Scar: a management dilemma. *La Radiologia Medica* **126**, 774–785 (2021).
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Vorgehen bei radiärer Narbe, komplexer sklerosierender Läsion (CSL)

	Oxford		
	LoE	GR	AGO
▪ **Radiäre Narbe / CSL in Stanz- oder Vakuumbiopsie:**			
▪ **Offene Biopsie**	3a	C	+
▪ **ohne Atypien**	3a	C	+
▪ **mit Atypien**	3a	C	++
▪ **Verzicht auf offene Biopsie, wenn Läsion klein (≤ 5 mm) oder in der Vakuumbiopsie bereits (weitgehend) vollständig enthalten**	5	C	+
▪ **Radiäre Narbe / CSL im Resektionsrand nach offener Exzision:**			
▪ **Keine Nachresektion**	3b	C	++

1. Donaldson, A. R., Sieck, L., Booth, C. N. & Calhoun, B. C. Radial scars diagnosed on breast core biopsy: Frequency of atypia and carcinoma on excision and implications for management. *Breast (Edinburgh, Scotland)* **30**, 201–207 (2016).
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5. Cohen, M. A. & Newell, M. S. Radial Scars of the Breast Encountered at Core Biopsy: Review of Histologic, Imaging, and Management Considerations. *Am J Roentgenol* **209**, 1168–1177 (2017).
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14. Woodward, S. G. *et al.* Is radial scar on core needle biopsy a risk factor for malignancy? A single-center retrospective review and implications for management. *Breast J* **26**, 2011–2014 (2020).
15. Liu, R. Q. *et al.* Upstage rate of radial scar/complex sclerosing lesion identified on core needle biopsy. *Am J Surg* **221**, 1177–1181 (2021).
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Brustkrebs-Früherkennung: Follow-up nach B3-Läsionen für Frauen im Alter zwischen 50 und 69 Jahren

	Oxford		
	LoE	GR	AGO
▪ **FEA, Papillom ohne Atypien, Radiäre sklerosierende Läsion**			
▪ **Screening-Mammographie**	5	C	++
▪ **LIN**			
▪ **Kurative Mammographie (12 Monate)**	3a	C	++
▪ **ADH**			
▪ **Kurative Mammographie (12 Monate)**	3a	C	++
▪ **Frauen mit LIN und ADH sind über ihr persönlich erhöhtes Brustkrebsrisiko zu informieren**	3a	C	++

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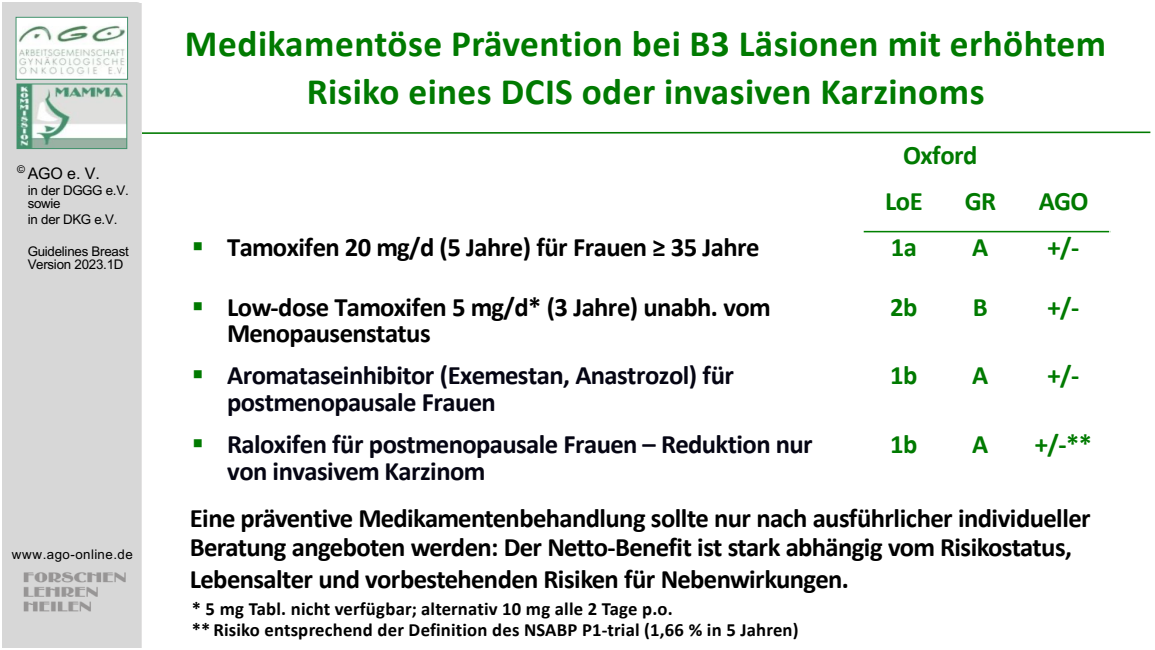

Medikamentöse Prävention bei B3 Läsionen mit erhöhtem Risiko eines DCIS oder invasiven Karzinoms

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen 20 mg/d (5 Jahre) für Frauen ≥ 35 Jahre	1a	A	+/-
▪ Low-dose Tamoxifen 5 mg/d* (3 Jahre) unabh. vom Menopausenstatus	2b	B	+/-
▪ Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen	1b	A	+/-
▪ Raloxifen für postmenopausale Frauen – Reduktion nur von invasivem Karzinom	1b	A	+/-**

Eine präventive Medikamentenbehandlung sollte nur nach ausführlicher individueller Beratung angeboten werden: Der Netto-Benefit ist stark abhängig vom Risikostatus, Lebensalter und vorbestehenden Risiken für Nebenwirkungen.

*** 5 mg Tabl. nicht verfügbar; alternativ 10 mg alle 2 Tage p.o.**
**** Risiko entsprechend der Definition des NSABP P1-trial (1,66 % in 5 Jahren)**

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