

# Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer

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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”)

- **Versions 2005–2017:**  
Albert / Audretsch / Brunnert / Fersis / Friedrich /  
Friederichs / Gerber / Kreipe / Nitz / Rody / Schreer /  
Sinn / Thomssen / Huober / Kreipe
- **Version 2018:**  
Friedrich / Sinn

# 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**

# B3-Lesions

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- 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, classic type (LN; ALH and LCIS)
  - 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

# Main types of B3-Lesions and Prospective Predictive Value (PPV) of Malignancy in Resection Specimen (DCIS/inv. Ca.)



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## B3-Lesions:

~PPV

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■ Atypical ductal hyperplasia (ADH)	20–30 %
■ Lobular intraepithelial neoplasia (LN/LIN)	0–10 %
■ Flat epithelial atypia (FEA)	0–10 %
■ Radial scar / Complex sclerosing lesion	0–10 %
■ Papilloma without atypia	0–10 %
■ Cellular fibroepithelial tumors / phyllodes tumors	0%

# Management after Minimally Invasive Biopsy

## Oxford

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- **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 +**

# Atypical ductal Hyperplasia (ADH)

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- **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.
- Classification in DIN 1 - 3 (ductal intraepithelial neoplasia grade 1 - 3) is not sufficiently validated.

# Strategy after Diagnosis of ADH in Biopsy Specimen

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## ADH in core- / vacuum-assisted biopsy:

→ Open excisional biopsy

→ Open excisional biopsy may be omitted, with:

- a) No mass-lesion radiologically, and
- b) a small lesion ( $\leq 2$  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

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Open excisional biopsy	3a	C	++
Open excisional biopsy may be omitted, with:			
a) No mass-lesion radiologically, and			
b) a small lesion ( $\leq 2$ TDLU*) in vacuum biopsy, and	5a	C	+/-
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



# Risk of Breast Cancer after Atypical Hyperplasy (ADH, ALH)

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## Stratification of breast cancer risk\*

■ Number of Foci:	1	RR = 2.65 (2.06-3.41)
	2	RR = 5.19 (3.59-7.52)
	≥ 3	RR = 8.94 (5.48-14.59)
■ Microcalcifications	present	RR = 3,21
	not present	RR = 4,21
■ Type	ductal	RR = 3,83
	lobular	RR = 3,67
	both	RR = 7,10
■ Age	< 45	RR = 6,76
	45–55	RR = 5,10
	> 55	RR = 2,67

# Lobular Intraepithelial Neoplasia (LIN)

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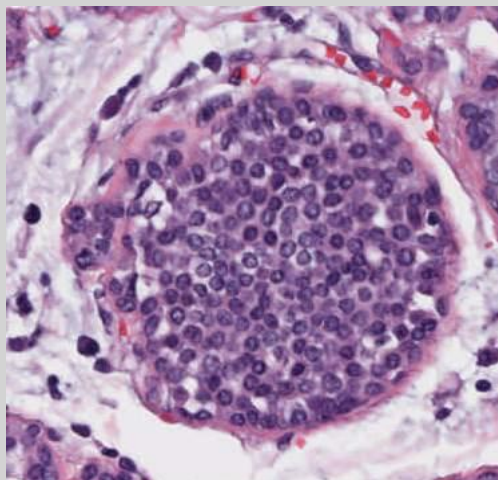
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- Includes: Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN 1 - 3 classification is not sufficiently validated prognostically
- Pleomorphic LIN and LIN with comedo-type necrosis are classified as premalignant → **B5a**
- Indicator/Precursor lesion:  
Ipsi- and contralaterally increased breast cancer risk:  
7 x after 10 years

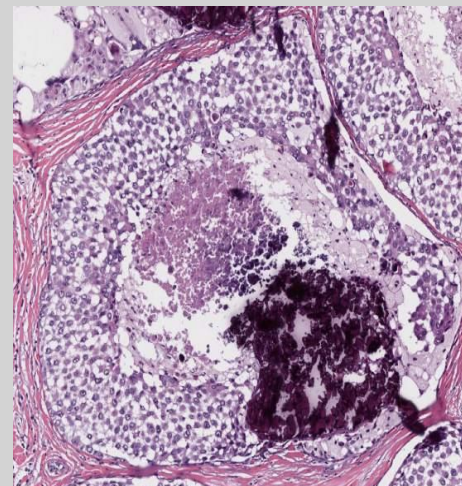
# Classical LIN and Variants of LIN with increased risk

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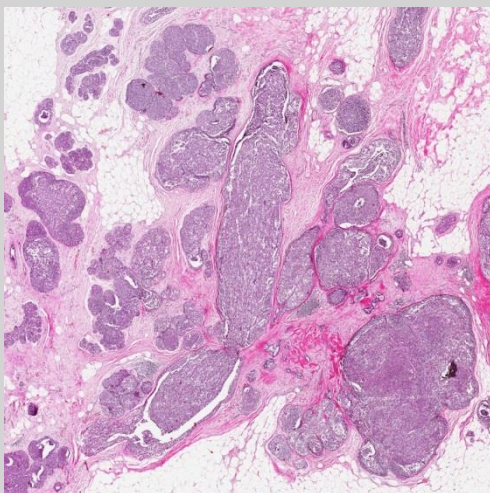
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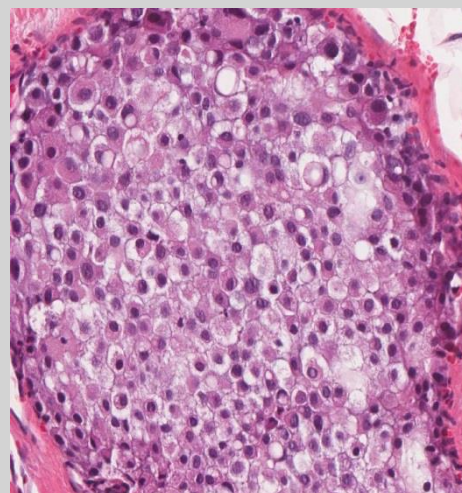
**Classical LIN**



**LIN with comedo type necrosis**



**Florid LIN**



**Pleomorphic LIN**

# LIN with High Risk

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- **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 neighbouring TDLU**
- **Type of LCIS with 21 cases of LCIS with microinvasion\*:**
  - classical LCIS: n=11
  - florid LCIS: n=4
  - pleomorphic LCIS: n=1

# Strategy after Diagnosis of LIN

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<ul style="list-style-type: none"> <li>■ <b><u>LIN in core- / vacuum-assisted biopsy:</u></b> <ul style="list-style-type: none"> <li>→ No further studies when LIN (classical variant) represents an incidental or isolated finding in core or vacuum biopsy and concordance in imaging</li> <li>→ Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings</li> </ul> </li> </ul>	2b	C	++
<ul style="list-style-type: none"> <li>■ <b><u>LIN at margins of resection specimen (BCT):</u></b> <ul style="list-style-type: none"> <li>→ No further surgery</li> </ul> </li> </ul>	2a	C	++
<ul style="list-style-type: none"> <li>■ <b><u>Exceptions:</u></b> <ul style="list-style-type: none"> <li>a) Pleomorphic LIN, florid LIN, or LIN with necrosis</li> <li>b) Imaging abnormality is not removed</li> <li>→ Complete resection</li> </ul> </li> </ul>	5	D	++

# Flat Epithelial Atypia (FEA)

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- **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. Therefore, histologic step sectioning and correlation with imaging are mandatory.

# Strategy after Diagnosis of FEA

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## ■ FEA in core biopsy/vacuum-assisted biopsy:

→ Open excisional biopsy may be omitted under the following circumstances:

a) a small lesion ( $\leq 2$  TDLU\* in vacuum biopsy)

**and**

b) Complete or near complete removal of imaging abnormality

**3b**      **C**      **+**

→ Representative open excisional biopsy in radiologically extensive microcalcifications or discordance to the radiological result

**5**      **C**      **+**

## ■ FEA at margins in resection specimen:

**3b**      **C**      **++**

→ No further surgery, unless calcifications have not been completely removed

\* Terminal ductal-lobular unit

# Papilloma

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- **Includes:** Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be **distinguished from** peripheral micropapilloma arising in the TDLU, size  $\leq 2$  mm, may be multiple
- To be distinguished from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Indicator lesion:**  
May be associated with in-situ or invasive cancer (in case of atypical papilloma up to 20%), increased ipsilateral risk for cancer (4.6% to 13% in case of atypical papilloma)



# Strategy after Diagnosis of Central Papilloma

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- **Papilloma without atypia in core needle or vacuum biopsy:**

- no further therapy, when biopsy sufficiently representative (100 mm<sup>2</sup>) and no discordance to imaging

Oxford		
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3a	C	++
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- **Multiple papillomas**

- open biopsy

3a	C	++
----	---	----

- **Papilloma with atypia in core needle or vacuum biopsies:**

- open biopsy

3a	C	++
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- **Papilloma at resection margin:**

- no published data available

# Radially Sclerosing Lesion

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- **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 radial-sclerosing lesion in core biopsy: 8.3% (79/948)\***

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

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- **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	+
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- **Radial scar / CSL at margins in resection specimen:**

- No further surgery

3b	C	++
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# Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

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<ul style="list-style-type: none"> <li>■ <b>FEA, non-atypical papilloma</b> <ul style="list-style-type: none"> <li>■ Screening mammography</li> </ul> </li> </ul>	5	C	++
<ul style="list-style-type: none"> <li>■ <b>LIN</b> <ul style="list-style-type: none"> <li>■ Mammography (12 months)</li> </ul> </li> </ul>	3a	C	++
<ul style="list-style-type: none"> <li>■ <b>ADH</b> <ul style="list-style-type: none"> <li>■ Mammography (12 months)</li> <li>■ Women with LIN and ADH should be informed about their elevated risk of breast cancer</li> </ul> </li> </ul>	3a	C	++

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

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■ Tamoxifen for women >35 years – Risk reduction of invasive BrCa and DCIS	1a	A	+
■ Aromatase inhibitors (Exemestan, Anastrozole) for postmenopausal women	1b	A	+/-
■ Raloxifen for postmenopausal women - Risk reduction of invasive BrCa only	1b	A	+/-*

Medical prevention should only be offered after individual and comprehensive counseling; the overall benefit is dependent on classification, age and pre-existing conditions that may influence the occurrence of side effects.

\* Risk situation as defined in NSABP P1-trial (1,66% in 5 years)

# Prevention for Lesions with Uncertain Biological Behavior (Tamoxifen)

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## NSABP-P2 Study, STAR trial 2006

	Placebo Rate / 1000 WE	Tamoxifen Rate / 1000 WE	RR	95% CI
All women	6.29	3.59	0.57	0.46-0.70
± LCIS	5.93	3.41	0.58	0.46-0.72
+ LIN	11.70	6.27	0.54	0.27-1.02
w/o ADH	5.87	3.69	0.63	0.50-0.78
+ ADH	10.42	2.55	0.25	0.10-0.52
5-year-risk <2%	4.77	3.18	0.67	0.43-1.01
5-year-risk > 5%	11.98	5.15	0.43	0.28-0.64
Relative 1. grade	6.47	3.48	0.54	0.34-0.83
> 3 relatives 1. grade	11.24	5.48	0.49	0.16-1.34
Fractures	2.88	1.97	0.91	0.51-0.92
Endometrial cancer	0.68	2.24	3.28	1.87-6.03

**Should only be offered to women with enhanced breast cancer risk (Gail  $\geq 1,66\%$ ):**

- LIN , with ADH
- Family history of breast cancer

**Should not be offered to women:**

- With moderate risk and > 50 year of age
- With enhanced risk for thrombembolism

# Prevention for Lesions with Uncertain Biological Behavior (Tamoxifen, Side Effects)

**Risks and Benefits with long-term Tamoxifen use compared with placebo:  
results from the IBIS-I Trial 96 months median follow-up  
(Cuzick J et al J Natl Cancer Inst 2007:272-282)**

Incidence	RR	95% CI	AR je 1000*	NNT / NNH**
Breast cancer	0.73	0.58-0.91	15	68
Invasive carcinoma	0.74	0.58-0.94	12	81
Thrombembolism	1.72	1.27-2.36	14	73
Deep vein thrombosis leg	1.84	1.21-2.82	9	115
Headache	0.93	0.87-0.99	25	39
Gynecological-/ vasomotoric symptoms	1.08	1.06-1.10	64	16
Chest pain	0.77	0.70-0.84	58	17

AR\*:Absolute risk per 1000 women. NNT/NNH\*\* = number needed to treat or number needed to harm

Data shown are statistically significant associations for a follow-up-period of 96 month.

Calculations by the authors of the guideline. Visvanathan K et al. JCO 2009;27:3235-3258.

# Prevention for Lesions with Uncertain Biological Behavior (Raloxifen)

## NSABP-P2 Study, STAR Trial 2006

	Tamoxifen: Rate / 1000 WE	Raloxifen Rate / 1000 WE	RR	95% CI
<b>All women</b>	<b>4.30</b>	<b>4.41</b>	<b>1.02</b>	<b>0.82-1.28</b>
<b>± LIN</b>	<b>3.76</b>	<b>3.89</b>	<b>1.03</b>	<b>0.81-1.33</b>
<b>+ LIN</b>	<b>9.83</b>	<b>9.61</b>	<b>0.98</b>	<b>0.58-1.63</b>
<b>± ADH</b>	<b>4.06</b>	<b>4.03</b>	<b>0.99</b>	<b>0.76-1.28</b>
<b>+ ADH</b>	<b>5.21</b>	<b>5.81</b>	<b>1.12</b>	<b>0.72-1.74</b>

Should only be offered to women with enhanced breast cancer risk :

- (Gail  $\geq$  1,66%) or postmenopausal

Should not be offered to women:

- With moderate risk > 50 year of age
- With enhanced risk for thromboembolism



# Prevention for Lesions with Uncertain Biological Behavior (Aromatase Inhibitors)

## Inclusion criteria:

## Results for prior ALH, ADH, LCIS (HR AI vs Plac):

### ■ IBIS.2:

- Prior ADH, ALH, or LCIS  
Anastrozole: 154 (8,0%);  
Placebo: 190 (9,7%)

- Yes (7J-MaCa-Risiko 12,1%):  
HR 0,31 (0,12–0,84)
- No (7J-MCa-Risiko 4,9%):  
HR 0,52 (0,31–0,78)

### ■ MAP.3:

- Prior ADH, ALH, or LCIS:  
Exemestane: 185 (8,1%);  
Placebo: 188 (8,3%)

- Yes: HR=0,61 (0,20–1,82)
- No: HR=0,26 (0,11–0,64)