Lesions of Uncertain Malignant Potential (B3)

(ADH, LIN, FEA, Papilloma, Radial Scar)
Lesions of Uncertain Malignant Potential (B3) (including “Precursor Lesions”)

- **Versions 2005–2015:**
  Albert / Audrethsch / Brunnert / Fersis / Friedrich / Gerber / Kreipe / Nitz / Rody / Schreer / Sinn / Thomssen

- **Version 2016:**
  Friederichs / Sinn
Pathology Reporting for Minimal Invasive Biopsies

B-Classification*

B1 = unsatisfactory / 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-Leitlinien
B3-Lesions

- Lesions with risk of associated DCIS or invasive Ca:
  - Atypical ductal hyperplasia (ADH)
  - Lobular neoplasia (ALH, LCIS)
  - Flat epithelial atypia (FEA)

- Inhomogenous lesions with sampling risk:
  - Phyllodes tumor, cellular fibroadenoma
  - Atypical papilloma, if incompletely removed
  - Radial scar, complex sclerosing lesion
**Major B3-Lesions and Prospektive Prediktive Value (PPV) for Malignancy in Resection**

<table>
<thead>
<tr>
<th>B3-Lesions</th>
<th>~PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical ductal hyperplasia (ADH)</strong></td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Lobular intraepithelial neoplasia (LN/LIN)</strong></td>
<td>0-10%</td>
</tr>
<tr>
<td><strong>Flat epithelial atypia (FEA)</strong></td>
<td>0-10%</td>
</tr>
<tr>
<td><strong>Radial scar / Complex sclerosing lesion</strong></td>
<td>0-10%</td>
</tr>
<tr>
<td><strong>Papilloma without atypia</strong></td>
<td>0-10%</td>
</tr>
<tr>
<td><strong>Cellular fibroepithelial tumors / phyllodes tumors</strong></td>
<td>0%</td>
</tr>
</tbody>
</table>
Management after Minimally Invasive Biopsy

Interdisciplinary conference: Concordant findings in pathology and imaging?

➔ yes: proceed according to histologic type 3a C ++

➔ no: open biopsy 3a C ++
Atypical Ductal Hyperplasia (ADH)

- **Synonyms:** Atypical intraductal epithelial proliferation (AIDEP), atypical epithelial proliferation of ductal type
- **Definition:** Atypical intraductal proliferations with cytologic 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 lumina 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 ductal intraepithelial neoplasia grade 1 - 3 is not sufficiently validated.**
Strategy after Diagnosis of ADH in Core Biopsy

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 (≤ 2 TDLU* in vacuum biopsy) and
  c) complete removal of imaging abnormality

ADH at margins in resection specimen:

→ No further surgery, if incidental finding accompanying invasive or intraductal carcinoma

Oxford / AGO LoE / GR
3a  C  ++
5a  C  +/-

* Terminal ductal-lobular unit
**Risk of Breast Cancer after Atypical Hyperplasie (ADH, ALH)**

### Stratification of breast cancer risk*

- **Number of Foci:**
  - 1: RR = 2.33
  - 2: RR = 5.26
  - ≥ 3: RR = 7.97

- **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

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Lobular Intraepithelial Neoplasia (LIN)

- **Includes:** Atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS
- LIN1 - 3 classification is not sufficiently validated prognostically
- Pleomorphic LIN and LIN with comedotype necrosis are classified as → **B5a**
- **Indicator/Precursor lesion:** Ipsilateral and contralateral enhanced breast cancer risk: 7 x at 10 years
Variants of Lobular Neoplasia

- Classical LIN
- Florid LIN
- LIN with comedo type necrosis
- Pleomorphic LIN
LIN with High Risk

- Pleomorphic LCIS: high grade cellular atypia, frequent involvement of ductules, comedo-type necroses, 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

- **LIN in core- / vacuum-assisted biopsy:**
  - Open excisional biopsy, with pleomorphic LIN, florid LIN, or LIN with comedo type necrosis or when not concordant with imaging findings

- **LIN at margins of resection specimen (BCT):**
  - No further surgery

**Exceptions:**
- a) Pleomorphic LIN, florid LIN, or LIN with necrosis
- b) Imaging abnormality is not removed

- Complete resection
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 → B5a

- **Marker lesion:**
  FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, histologic step sectioning and correlation with imaging are mandatory.
Strategy after Diagnosis of FEA

➤ **FEA in core biopsy/vacuum-assisted biopsy:**
  → Open excisional biopsy
  → Open excisional biopsy may be omitted, with:
    a small lesion (≤ 2 TDLU* in vacuum biopsy) and complete removal of imaging abnormality

➤ **FEA at margins in resection specimen:**
  → No further surgery, unless calcifications have not been completely removed

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Oxford / AGO LoE / GR

3b C +

5 C +

3b C ++

---

* Terminal ductal-lobular unit
Papilloma

- **Includes:** Central and peripheral papilloma > 2 mm, atypical intraductal papilloma (B3)
- To be discriminated from peripheral micropapilloma arising in the TDLU, size ≤ 2 mm, may be multiple
- To be discriminated from papilloma with DCIS, from intraductal papillary carcinoma, and from encapsulated papillary carcinoma
- **Indicator lesion:** May be associated with in-situ or invasive cancer (10%, 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

- Papilloma without atypia in core needle or vacuum biopsies:
  - no further therapy, when biopsy sufficiently representative (100 mm²) and no discordance to imaging

- Multiple papillomas
  - open biopsy

- Papilloma with atypia in core needle or vacuum biopsies:
  - open biopsy

- Papilloma at resection margin:
  - no published data available
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 radial-sclerosing lesion in core biopsy: 8.3% (79/948)*

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

- **Radial scar / CSL in core biopsy/vacuum-assisted biopsy:**
  - Open excisional biopsy
  - Open excisional biopsy may be omitted, with a small lesion and complete removal of imaging abnormality

- **Radial scar / CSL at margins in resection specimen:**
  - No further surgery

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b C +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a C +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b C ++</td>
<td></td>
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</tr>
</tbody>
</table>
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions

**FEA, non-atypical papilloma**
- Screening mammography  

**LIN**
- Mammography (12 months)

**ADH**
- Mammography (12 months)

- Women with LIN and ADH should be informed about their elevated risk of breast cancer

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>5</th>
<th>C</th>
<th>++</th>
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</thead>
<tbody>
<tr>
<td>LIN</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>ADH</td>
<td>3a</td>
<td>C</td>
<td>++</td>
</tr>
</tbody>
</table>
Medical Prevention for Women at Increased Risk (including Women with LIN and ADH)

- Tamoxifen for women >35 years –
  Risk reduction of invasive BrCa and DCIS
  1a A +

- Raloxifene for postmenopausal women -
  Risk reduction of invasive BrCa only
  1b A +/-*

- Aromatase inhibitors (Exemestan, Anastrozole)
  for postmenopausal women
  1b A +/-

Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age and pre-existing risk factors for side effects.

*Risk situation as defined in NSABP P1-trial (1,66% in 5 years)
Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen)

NSABP-P1 Study, update 2005

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

Should only be offered to women with enhanced breast cancer risk (Gail ≥1,66%):

- LIN, ADH
- Family history of breast cancer

Should not be offered to women:

- With moderate risk > 50 year of age
- With enhanced risk for thrombembolism
Medical Prevention after Diagnosis of B3 Lesion (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)

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

AR*: Absolute risk per 1000 women. NNT/NNH** = number needed to treat or number needed to harm: shown are statistically significant associations for a follow-up-period of 96 month.

Visvanathan K et al. JCO 2009;27:3235-3258.
Medical Prevention after Diagnosis of B3 Lesion (Raloxifene)

NSABP-P2 Study, STAR trial 2006

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

Should only be offered to women with enhanced breast cancer risk:
(Gail ≥1,66%) or postmenopausal

Should not be offered to women:
• With moderate risk > 50 year of age
• With enhanced risk for thrombembolism
# Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors)

## Inclusion criteria:

### IBIS.2:
- Prior ADH, ALH, or LCIS
  - Anastrozole: 154 (8.0%)
  - Placebo: 190 (9.7%)

### MAP.3:
- Prior ADH, ALH, or LCIS:
  - Exemestane: 185 (8.1%)
  - Placebo: 188 (8.3%)

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes (7y-BC-risk 12.1%)</th>
<th>No (7y-BC-risk 4.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBIS.2</td>
<td>HR 0.31 (0.12–0.84)</td>
<td>HR 0.52 (0.31–0.78)</td>
</tr>
<tr>
<td>MAP.3</td>
<td>HR=0.61 (0.20–1.82)</td>
<td>HR=0.26 (0.11–0.64)</td>
</tr>
</tbody>
</table>

Lesions of Uncertain Malignant Potential (B3) (2/25)

Pubmed 2010-2015 (plus earlier publications if relevant):


Screened Guidelines:

- Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Aktualisierung 2012
- NCCN Breast cancer V.I.2014
- NCCN Breast Cancer Risk Reduction I 2013
- NCCN Breast Cancer Screening and Diagnosis 2.2013
- NZ: HTA risk assessment 2007
- CMJA: no update
- NICE: no update
- SIGN: no update
- Cochrane: Decision aids for risk communication update 2009
- DARE: no relevant references. 2010
- ASCO 2012: done
- National Institute of Health (NIH): done
- San Antonio Breast Cancer Conference (SABCC 2013): done

References

National and international guidelines
Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL
National and international guidelines
Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V. (Hrsg.). Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL
Pathology Reporting for Minimal Invasive Biopsies (3/25)

Further information:

The histologic B-classification of breast core biopsies as based on recommendations of the National Coordinating Group for Breast Screening Pathology (NHSBSP), and E. C. Working Group on breast screening pathology encompasses the heterogeneous B3 category.

References:

B3-Lesions (4/25)

Further information:

Lesions of uncertain malignant potential include atypical ductal hyperplasia (ADH), lobular neoplasia (LN), flat epithelial atypia (FEA), atypical papillary proliferations, and lesions with sampling risk because of inhomogeneity, such as phyllodes tumor, cellular fibroadenoma, and radial scars. The lesions with atypical proliferations (ADH, ALH, LCIS, FEA) are regarded both as an indicator of increased risk, but also as precursor lesions, and are part of the low-grade pathway of breast cancers [1-4]. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient, and to decide if the lesion should be excised. The recognition of atypical epithelial proliferation is based on the distinction of hyperplastic from neoplastic lesions, that is on the identification of a clonal process. As a general rule, usual type epithelial hyperplasia is morphologically and phenotypically heterogeneous, while ADH, FEA, and LN are characterized by a homogeneity of cell type and marker expression. With all types of precursor lesions, careful attention must be paid to the pathologic-radiologic correlation for the guidance of the clinical management. B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1,3% discordance for B5 lesions [5].

References:


Further information:

In this category atypical intraductal hyperplasia (ADH), flat epithelial atypia (FEA), and lobular intraepithelial neoplasia (LN/LIN) are grouped together as lesions of uncertain biological behaviour. Besides these diagnoses papillomas, radial scar and phyllodes-tumour belong to the B3 group. In older studies approximately one-third of CNB results classified as B3 were malignant on excision, but the likelihood of malignancy varied substantially between specific lesion groups. Whereas cases may be selectively managed without surgery, the majority warrant excision biopsy (Rakha 2010, Houssami 2010). No clinical and radiologic findings and/or comprehensive evaluation of multiple histologic parameters on CNB specimen are distinctive enough to predict final classification of equivocal cellular fibroepithelial lesions. In recent years publications demonstrated a decline in PPV except for ADH. This is particularly obvious for LIN, which only rarely shows upgrade to higher lesions in resection when careful correlation between imaging and histology of CNB has been performed. Also papilloma without atypia usually shows no upgrade in resection. With regard to FEA different frequencies of upgrade to higher lesions are published. B3 lesions are diagnosed with less than 10% in mammography screening (6000 core biopsies, with central pathology). But B3 lesions are associated with a high rate of 6-16% discordance among first and second pathology compared to 0.5-1.3% discordance for B5 lesions (Kreipe HH et al 2008).

Current systematic review:
Other References:


Management after Minimally Invasive Biopsy (6/25)

Further information:

What kind of treatment has to follow when a B3 diagnosis has been rendered should be individually determined in an interdisciplinary discussion of the imaging findings and the pathology results. Algorithm for quality assurance of minimal invasive guided biopsies.

After a review and quality assessment of 21 studies, diagnostic accuracy of VAB were evaluated. The summary estimates for VAB in diagnosis of breast carcinoma were as follows: sensitivity, 0.981 (95% confidence interval [CI], 0.972-0.987); specificity, 0.999 (95% CI, 0.997-0.999); positive likelihood ratio (PLR), 93.84 (95% CI, 41.55-211.95); negative likelihood ratio, 0.05 (95% CI, 0.03-0.09); diagnostic odds ratio, 1891.7 (95% CI, 683.8-5233.4); underestimate rate of ADH and DCIS were 20.9% (95% CI, 0.177-0.245) and 11.2% (95% CI, 0.098-0.128), respectively. VAB is a highly sensitive and specific biopsy method for evaluating mammographically detected breast in women.

References:


**Atypical Ductal Hyperplasia (ADH) (7/25)**

*Further information:*

ADH and breast cancer are associated with postmenopausal hormone treatment. According to the data of the Breast Cancer Surveillance Consortium (USA) rates of ADH decreased from 5.5/10000 mammograms 1999 to 2.4/10000 mammograms in 2005.

*Statement: indicator-/ precursor-lesion:*

Women have an enhanced breast cancer risk after ADH: one lesion RR 3.88 (95%CI 3.00-4.94), three lesions RR10.35 (95%CI 6.13-16.4). Less than 45 years at diagnosis of ADH RR 6.78 (95%CI 3.24-12.4).

*References:*

**Strategy after Diagnosis of ADH (8/25)**

*Further information:*
Significant histologic predictors of upgrade from ADH to carcinoma included number of terminal duct-lobular units (TDLU; >2) involved (P = .0306), presence of significant cytologic atypia suspicious for intermediate or high-grade carcinoma (P < .0001), and necrosis (P = .0006). Therefore, ADH lesions with significant cytologic atypia and/or necrosis are most likely to be associated with carcinoma and should be excised. ADH without these features, regardless of extent of involvement, and with complete removal of the targeted calcifications, is associated with a minimal risk (<3%) of carcinoma and may undergo mammographic follow-up only (Nguyen CV 2010, Allison KH 2010). Radiological calcification with suspicious or malignant characteristics and histological B3 with evidence of epithelial atypia has the highest positive predictive value (50%) (Rhaka et al. 2010). Even in the case of complete removal of microcalcifications there is a risk of 5% of underestimation of malignancy (Penco 2010). An open excisional is recommended with exception of very small lesions (≤ 2 TDLU) and minimal atypia and complete removed imaging abnormality. ADH in core- / vacuum-assisted biopsy (LoE 3a) ADH at margins in resection specimen (LoE 3a)

*References:*
Risk of Breast Cancer after Atypical Hyperplasia (ADH, ALH) (9/25)

No further information

References:

**Lobular Intraepithelial Neoplasia (LIN) (10/25)**

*Further information:*

Lobular neoplasia (LN) or lobular intraepithelial neoplasia (LIN) are the preferred terms for early neoplasia with lobular phenotype and include atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). For a long time, LN was considered to be just as a risk indicator and not a precursor lesion for the subsequent development of carcinoma. More recently, because of pathological and molecular studies, it is now believed that lobular neoplasia indeed is a non-obligatory precursor of invasive carcinoma, and at the same time a risk lesion for ipsi- and contralateral disease. Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, florid LCIS and pleomorphic LCIS were shown to be behave more aggressively compared to classical lobular neoplasia. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. After diagnosis of LIN on core needle, or on vacuum-assisted biopsy, the average upgrade rate is about 15%. The management of lobular neoplasia in excisional biopsies by the pathologist requires attention to the following points: 1) He should be aware of the risk of occult microinvasion and pay attention to the careful workup of the specimen. 2) In cases of pleomorphic LCIS attention must be paid to the margin status like in low-grade DCIS, to make sure that florid or pleomorphic LN has be completely excised. 3) The metric extent of LN should be determined approximately by the pathologist since extensive LN may be associated with a higher risk and to help correlate the findings with the radiologic findings. Lobular Intraepithelial Neoplasia (LIN; atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long the criteria for pleomorphic LIN and LIN with necrosis are not fulfilled which qualify for B5a.
References:


Statement: Indicator-/ precursor lesion
Variants of Lobular Neoplasia (11/25)

Further information:

Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, pleomorphic lobular carcinoma in situ (pLCIS) was shown to be behave more aggressively compared to classical lobular neoplasia (1). The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. In this respect pLCIS mimics ductal carcinoma in situ (DCIS), but characteristically it is associated with classical LN and not with DCIS. Also, molecular profiling studies have shown that pLCIS is similar to classical LN, supporting its role as a special form of lobular neoplasia. As another approach for risk assessment, a classification of lobular neoplasia into three different grades of severity has been proposed, based on the extent of lobular cancerization (2). The most severe grade (LIN 3) is called florid lobular carcinoma in situ nowadays (3).

References:

LIN with High Risk (12/25)

Further information:

Several different morphologic variants of lobular neoplasia have been described to more precisely evaluate the individual risk. Specifically, pleomorphic lobular carcinoma in situ (pLCIS) was shown to be behave more aggressively compared to classical lobular neoplasia [1]. The distinction of pLCIS from classical LN relies on nuclear characteristics with pLCIS having larger, more pleomorphic nuclei with obvious nucleoli, and may show apocrine differentiation, necrosis and microcalcifications. In this respect pLCIS mimics ductal carcinoma in situ (DCIS), but characteristically it is associated with classical LN and not with DCIS. Also, molecular profiling studies have shown that pLCIS is similar to classical LN, supporting its role as a special form of lobular neoplasia. As another approach for risk assessment, a classification of lobular neoplasia into three different grades of severity has been proposed, based on the extent of lobular cancerization [2]. The most severe grade (LIN 3) is called florid lobular carcinoma in situ nowadays [3]. It may be associated with microinvasion [4].

References:

Strategy after Diagnosis of LIN (13/25)

Further information:

In contrast to atypical ductal hyperplasia, it is less clear if a follow-up excisional biopsy is beneficial to the outcome of a patient with the finding of lobular neoplasia in the core biopsy, and therefore there is some disagreement if excision should be recommended as a rule or not. This is mainly due to the relative infrequency of lobular neoplasia as the most severe finding in core biopsies and the even lower number of excisional biopsies in this situation. Not surprisingly these small studies have led to widely discrepant results and conflicting interpretations of published data. An excisional biopsy was recommended in fully developed LCIS because of an upgrade rate of greater than of 25% [1] or 16% [2], but results were inconclusive with lesions of lesser extent, namely atypical lobular hyperplasia. The argument against a routine follow-up biopsy is that LN as the most significant pathology usually is an incidental finding in an otherwise benign core biopsy and if there is no other clinical or radiological detectable lesion, it is unlikely that an excisional biopsy could yield anything more significant [3]. This argument has to be taken seriously, and at least all cases with LCIS and a mass lesion should be followed up by a surgical biopsy. However, because of the reported upgrade rates in fully developed LCIS, the nature of these lesions as non-obligate precursors, and risk of missing a radiologically occult invasive cancer, an open biopsy in classical LCIS should be considered as an option also [2], especially if multiple lobules are involved.

References:

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


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

Flat Epithelial Atypia (FEA) (14/25)

Further information:

FEA represents one of the earliest morphologically recognizable neoplastic alterations of the breast. It is characterized by mildly to severely atypical cells simply replacing the single layer of native epithelial cells in a flat fashion without appreciable proliferation.

Marker Lesion

FEA is highly associated with microcalcification (77%). The mammographic features are amorphous and pleomorphic microcalcification. In about one-third to one-quarter of cases of FEA seen at core biopsy, a more advanced lesion is found at excision: ADH, DCIS and tubular carcinoma. A 2- to 3-fold increase in the occurrence of ADH in the presence of FEA versus in their absence (P < .005) was observed. A finding of FEA on benign breast biopsy may indicate the presence of ADH, a more worrisome lesion (Boulos FI). FEA might be associated with noninvasive cancer but not with invasive cancer.

References:

Statement: Marker Lesion (LoE 3b)

1. Kunju L: Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? Hum Pathol 2006; 38:35-41
2. Noske A: Flat epithelial atypia is a common subtyp of B3 breast lesions and associated with noninvasive cancer but not with invasive cancer in final excision histology. Hum Pathol 2009; Epub ahead of print.
Strategy after Diagnosis of FEA (15/25)

Further information:

If a FEA is detected in core biopsy further no further (open) biopsy is indicated if the underlaying lesion / calcification is completely removed (Lee TJ, 2010). In cases of FEA combined with an ADH further surgery depends on the ADH lesion (Ingegnoli A, 2010).

Statement: FEA in core (LoE 3a)
Statement: FEA at margins in resection specimens (LoE 3b)

References:


Further information:

Benign intraductal papillomas occur either as a central papilloma originating from the ducts in the subareolar region, or peripherally, and both locations can be either solitary or multiple. Both central and peripheral papillomas are characterized by fibrovascular cores with epithelial and myoepithelial cell layers. Central intraductal papillomas with a predominant or exclusive glandular differentiation are called ductal adenoma [1]. Intraductal papillomas and ductal adenomas may show regressive changes, such as sclerosis or infarction, also also epithelial or myoepithelial hyperplasia or squamous or apocrine metaplasia. These changes may cause diagnostic difficulties in core needle biopsy [2]. The term papillomatosis is not used in the WHO classification of the breast, because was historically used both for usual type ductal hyperplasia and for papillomas.

Atypical epithelial proliferations (ADH and DCIS) may occur in papillomas, and are usually of low grade. As with atypical intraductal proliferative lesions, the distinction of ADH and DCIS within a papilloma rests with quantitative criteria [1]. An intraductal papilloma with ADH is diagnosed when the atypical epithelial proliferation is \(< 3\) mm, while larger atypical epithelial proliferations within a papilloma fulfill the criteria of an intraductal papilloma with low grade [3]. This definition replaces alternative terminologies that were focused on the proportion of atypical cells (30% or 90%) within a papilloma. An intermediate or high grade DCIS within a papilloma can be diagnosed regardless of the extent of atypia.

References:

Further information:

A policy of open excisional biopsy after the diagnosis of a central papilloma has been recommended by the European guidelines for quality assurance in breast cancer screening. However, this recommendation has been questioned by newer studies. The risk of up-grade is to be considered very low in central papilloma without atypia and not sufficient to justify routine surgical resection.

References:


Radially Sclerosing Lesion (18/25)

References
Strategy after Diagnosis of Radial Scar, Complex Sclerosing Lesion (CSL) (19/25)

References
Follow-up Imaging for Women Age 50-69 Years with B3-Lesions (20/25)

Further information:

Women with ADH and LIN need to be informed about their elevated risk for breast cancer. Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolute terms, helping women to make an informed decision to her personal needs and values. Atypia patients who drank alcohol and had a first-degree relative with breast cancer have an increased risk of breast cancer compared to those without atypia [1].

References:

Medical Prevention for Women at Increased Risk (including Women with LIN and ADH) (21/25)

Further information:

Risk communication should provide women with information of risk reduction strategies (e.g. follow-up or medical intervention) providing comprehensive disclosure of risks and benefits in absolut terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

References:


Studies on medical prevention for women at increased risk that included women with LIN and ADH are in bold.
Tamoxifen für Frauen > 35 Jahre – Reduktion von DCIS und invasivem Karzinom (LoE 1a A AGO +)

NSABP.P1:


IBIS.1


Royal Marsden
Italian Trial

Aromataseinhibitor (Exemestan, Anastrozol) für postmenopausale Frauen (LoE 1b A AGO +/-)

MAP.3


Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen) (22/25)

No further information

References:

Medical Prevention after Diagnosis of B3 Lesion (Tamoxifen, Side Effects) (23/25)

*Further information:*

Risk communication should provide women with information of risk reduction strategies (e.g. follow-up and medical intervention) providing comprehensive disclosure of risks and benefits in absolut terms (numbers needed to treat and numbers needed to harm), helping women to make an informed decision to her personal needs and values.

*References:*

Medical Prevention after Diagnosis of B3 Lesion (Raloxifen) (24/25)

No further information

References:

Prevention for Lesions with Uncertain Biological Behaviour (Aromatase Inhibitors) (25/25)

No further information

References:

Exemestane for breast-cancer prevention in postmenopausal women.


Chemoprevention for breast cancer.

1. Bozovic-Spasojevic I, Azambuja E, McCaskill-Stevens W, Dinh P, Cardoso F.