Atypical Lesions:
To Excise or Not To Excise?

H. Evin Gulbahce MD
Needle Guided Biopsy

Excisional biopsy
Sterotactic Core Biopsy
<table>
<thead>
<tr>
<th>Type</th>
<th>Used For</th>
<th>Needle</th>
<th>Anesthesia</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine needle aspiration (FNA)</td>
<td>Cysts, masses</td>
<td>22 or 25 G</td>
<td>Local or none</td>
<td>Fast, no stitch, no scar</td>
<td>Small sample size, operator dependent</td>
</tr>
<tr>
<td>Core Needle</td>
<td>Solid mass, Ca++</td>
<td>10,11,14 G</td>
<td>Local</td>
<td>No stitch, no internal scar</td>
<td>Limited sample size</td>
</tr>
<tr>
<td>Vacuum Assisted (Mammotome)</td>
<td>Mass, Ca++</td>
<td>9, 11,14 G, 0.25 inch incision</td>
<td>Local</td>
<td>Excellent for Ca++, no stitches, min scar</td>
<td>Not good for hard to reach lesions</td>
</tr>
<tr>
<td>Large Core Surgical (ABBI)</td>
<td>Nonpalpable</td>
<td>5mm-20mm, size of wine cork</td>
<td>Local</td>
<td>Large tissue without sedation</td>
<td>Stitches, scar, may not have adequate margin</td>
</tr>
<tr>
<td>Open Surgical</td>
<td>Hard to reach</td>
<td>1.5-2 in incision, golf ball size</td>
<td>Heavy sedation or general anesthesia</td>
<td>Large tissue, accurate diagnosis</td>
<td>Permanent scar, stitches, longer recovery</td>
</tr>
</tbody>
</table>
BIRADS Breast Imaging Reporting and Data System

0: Incomplete
1: Negative
2: Benign finding(s)
3: Probably benign (≤2% risk of malignancy)
4: Suspicious abnormality
5: Highly suggestive of malignancy
6: Known biopsy – proven malignancy
Wire localization / excisional biopsy versus image guided / sterotactic core biopsy

**Excisional Bx**
- Surgical excision
- Done in OR, more $$
- 70% need second surgery

**Core Bx**
- Stab wound to insert needle
- Outpatient, local anesthesia, less $$
- 84% only one surgery
- No permanent effect in subsequent mammograms
Breast Needle Biopsy

- Anything can turn up..
- What you see is what you have and it may not be all there is..
- What you have may be all there is..
High Risk Lesions

- Atypical Ductal Hyperplasia (ADH)
- Lobular Neoplasia (ALH + LCIS)
- Flat Epithelial Atypia (FEA)
- Radial Scar or Complex Sclerosing Lesions
- Papilloma
“Underestimation”
“Upgrade in excision”

Missing a lesion that would have otherwise required additional surgery
- Invasive cancers
- DCIS
Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.

Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to pathologist.
Predictors of Malignancy on Excision Depends on

- As the technology to obtain image guided breast tissue changes, and the amount of breast tissue removed increases, the need for re-excision may be re-evaluated.

- Volume of breast tissue removed:
  - 14 Gauge needle: 17 mg
  - 14 Gauge vacuum-assisted device: 36 mg
  - 11 Gauge vacuum-assisted device: 94 mg

- Complete removal
  - Related to biopsy type / needle size

- Underestimation for ADH
  - 20-56% with 14G needle vs 0-38% vacuum assisted 11G or 14G

Bauer, Breast J 2003
Liberman Rad Clin North Am, 2000
Studies Involving High Risk Lesions

- Retrospective, small numbers
- Coexistence of >1 high risk lesion
- Selection criteria for surgical excision unknown and / or not uniform
- Lack of follow up data from patients not referred to excision
- Variability in pathologic diagnosis of high risk lesions
Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

• Registrants to a Radiology Meeting given cases and responses were reported
• Information on radiologic findings, type/gauge of bx, number of bx cores, adequacy of sampling (e.g. adequate sampling of calcifications), pathologist Dx provided.
• Asked for recommendation

Georgian-Smith et al AJR 2012
**Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion**

**TABLE 2: Registrant Responses for Lobular Carcinoma In Situ (LCIS)**

<table>
<thead>
<tr>
<th>Response</th>
<th>2010 (86)</th>
<th>2011 (34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant; imaging follow-up</td>
<td>12 (14)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Concordant but because of LCIS; recommend surgery</td>
<td>57 (66)</td>
<td>19 (56)</td>
</tr>
<tr>
<td>Discordant because LCIS is incidental without imaging correlate; recommend surgery</td>
<td>17 (20)</td>
<td>11 (32)</td>
</tr>
</tbody>
</table>

Note—Data in parentheses are percentages.

Georgian-Smith et al AJR 2012
Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

They were updated in the literature asked what their management will be

Georgian-Smith et al AJR 2012
Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

They were updated in the literature asked what their management will be.

### TABLE 6: Summary of Options

<table>
<thead>
<tr>
<th>Option</th>
<th>Respondent Answers (83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will not change</td>
<td>35 (42)</td>
</tr>
<tr>
<td>Definitely change</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Will consider changing</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Now completely confused</td>
<td>28 (34)</td>
</tr>
</tbody>
</table>

Note—Data in parentheses are percentages.

Georgian-Smith et al AJR 2012
### Management Practice of Borderline Lesions on Needle Biopsy

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Routine excision, n (%)</th>
<th>Selective excision, n (%)</th>
<th>No further excision, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>405 (85)</td>
<td>63 (13)</td>
<td>NA</td>
</tr>
<tr>
<td>Lobular neoplasia</td>
<td>270 (57)</td>
<td>144 (30)</td>
<td>52 (11)</td>
</tr>
<tr>
<td>Radial scar</td>
<td>273 (57)</td>
<td>192 (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Papillary lesion</td>
<td>235 (49)</td>
<td>216 (45)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Flat epithelial atypia</td>
<td>274 (57)</td>
<td>148 (31)</td>
<td>47 (10)</td>
</tr>
</tbody>
</table>

NA = not applicable.
## Management Practice of Borderline Lesions (Margin)

### Table 3: Management of ADH found on margin of specimen

<table>
<thead>
<tr>
<th>Variable</th>
<th>No further surgery (n = 263), n (%)</th>
<th>Selective reexcision (n = 130), n (%)</th>
<th>Routine reexcision (n = 22), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in tumor board</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>150 (68)</td>
<td>62 (28)</td>
<td>6 (3)</td>
<td>.006*</td>
</tr>
<tr>
<td>Biweekly</td>
<td>63 (65)</td>
<td>30 (31)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>35 (48)</td>
<td>28 (38)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (54)</td>
<td>10 (36)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Fellowship training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical oncology</td>
<td>40 (68)</td>
<td>18 (31)</td>
<td>1 (2)</td>
<td>.03†</td>
</tr>
<tr>
<td>Breast</td>
<td>151 (60)</td>
<td>80 (32)</td>
<td>17 (7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>58 (73)</td>
<td>20 (25)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (48)</td>
<td>12 (41)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Annual volume of new breast patients</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>&lt;25</td>
<td>16 (38)</td>
<td>20 (48)</td>
<td>5 (12)</td>
<td></td>
</tr>
<tr>
<td>25–50</td>
<td>47 (48)</td>
<td>43 (44)</td>
<td>7 (7)</td>
<td></td>
</tr>
<tr>
<td>51–100</td>
<td>67 (61)</td>
<td>37 (34)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>133 (79)</td>
<td>30 (18)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Percentage of practice dedicated to breast surgery</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>&lt;15%</td>
<td>8 (50)</td>
<td>6 (38)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>15%–50%</td>
<td>45 (46)</td>
<td>44 (45)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>210 (26)</td>
<td>80 (69)</td>
<td>12 (4)</td>
<td></td>
</tr>
<tr>
<td>Type of practice</td>
<td></td>
<td></td>
<td></td>
<td>.0009†</td>
</tr>
<tr>
<td>Cancer center</td>
<td>32 (80)</td>
<td>8 (20)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>124 (54)</td>
<td>92 (40)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>54 (72)</td>
<td>17 (23)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Dedicated breast center</td>
<td>53 (72)</td>
<td>13 (18)</td>
<td>6 (8)</td>
<td></td>
</tr>
</tbody>
</table>

*Nizri et al Am J Surgery 2012*
## Management Practice of Borderline Lesions (Margin)

### Table 4: Management of lobular neoplasia found at a margin of excisional specimen

<table>
<thead>
<tr>
<th>Participation in tumor board</th>
<th>No further surgery (n = 316), n (%)</th>
<th>Selective reexcision (n = 123), n (%)</th>
<th>Routine reexcision (n = 19), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td>157 (72)</td>
<td>54 (25)</td>
<td>6 (3)</td>
<td>.02*</td>
</tr>
<tr>
<td>Biweekly</td>
<td>74 (76)</td>
<td>22 (23)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>45 (62)</td>
<td>21 (29)</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (54)</td>
<td>10 (36)</td>
<td>3 (11)</td>
<td></td>
</tr>
<tr>
<td>Fellowship training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical oncology</td>
<td>48 (81)</td>
<td>10 (17)</td>
<td>1 (2)</td>
<td>.008†</td>
</tr>
<tr>
<td>Breast</td>
<td>56 (71)</td>
<td>21 (27)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13 (45)</td>
<td>15 (52)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>174 (70)</td>
<td>61 (24)</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>Annual volume of new breast patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>20 (48)</td>
<td>17 (40)</td>
<td>5 (12)</td>
<td>.002*</td>
</tr>
<tr>
<td>25–50</td>
<td>63 (65)</td>
<td>27 (28)</td>
<td>7 (7)</td>
<td></td>
</tr>
<tr>
<td>51–100</td>
<td>80 (73)</td>
<td>29 (27)</td>
<td>0 (1)</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>128 (76)</td>
<td>34 (20)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Percentage of practice dedicated to breast surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15%</td>
<td>9 (56)</td>
<td>4 (25)</td>
<td>3 (19)</td>
<td>.0001*</td>
</tr>
<tr>
<td>15%–50%</td>
<td>57 (58)</td>
<td>31 (32)</td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>225 (774)</td>
<td>72 (24)</td>
<td>4 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Nizri et al Am J Surgery 2012
Columnar Cell Lesions of the Breast and Flat Epithelial Atypia (FEA)
Currently Used Terminology for Columnar Cell Lesions of the Breast

- Columnar Cell Change
- Columnar Cell Hyperplasia
- Columnar Cell Change with Atypia (Flat Epithelial Atypia)
- Columnar Cell Hyperplasia with Atypia (Flat Epithelial Atypia)

**Not uncommon to see a combination of these in a breast biopsy**

**These lesions also often coexist with areas that are diagnostic for ADH or DCIS and therefore, search for these significant findings should be conducted upon identification of columnar cell lesions.**

Schitt Adv Anat Pathol 2003
Turashvili Virchows 2008
Feeley Histopathology 2008
Columnar Cell Change

- Terminal duct lobular units (TDLU) with dilated acini, usually with irregular contours.
- Lined by one or two layers of columnar epithelium with uniform, ovoid to elongated nuclei.
- Apical cytoplasmic blebs often but not prominent at the luminal surface.
- Intraluminal secretions may be present in the lumina associated with luminal calcifications.
Columnar Cell Hyperplasia

- TDLU with variably distended acini often with irregular contours.
- Cellular stratification more than two cell layers.
- Apical snouts present, often exaggerated.
- Luminal secretions often present, associated with calcification which may be psammomatous.
- **NO COMPLEX ARCHITECTURAL PATTERN**
Flat Epithelial Atypia

- Similar to architectural features of columnar cell change or columnar cell hyperplasia but with **subtle cytologic atypia**
- Round or ovoid (rather than elongated) nuclei that are **not oriented perpendicular** to the basement membrane with somewhat increased nuclear cytoplasmic ratio.
- **Nucleoli** may be variably prominent.
Flat Epithelial Atypia

not allowed

**Architecture**
- Complex architectural patterns
  - Well developed micropapillations
  - Bridges or sieve like fenestrations
- If present, these lesions should be characterized as ADH or DCIS depending on the severity and extent.

**Cytology**
- High grade cytologic atypia or nuclear pleomorphism that is seen in high grade DCIS, even if only one cell layer thick

Schnitt, Adv Anat Path 2003
Flat Epithelial Atypia

Differential Diagnosis

• **Cytologic**
  – Microcysts
  – Apocrine metaplasia
  – Columnar Cell Change / Hyperplasia

• **Architectural**
  – ADH
  – Low grade DCIS

Need to go to High Power

Low Power

Schnitt, Adv Anat Path 2003
<table>
<thead>
<tr>
<th></th>
<th>FEA</th>
<th>ADH / DCIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade cytologic atypia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Complex architectural patterns</td>
<td>NO</td>
<td>+</td>
</tr>
<tr>
<td>High-grade atypia</td>
<td>NO</td>
<td>-/+</td>
</tr>
</tbody>
</table>
Biologic Markers of Columnar Cell Lesions of the Breast

- Intense ER and PR positivity

- Rare mitosis and Ki-67 positivity, even in those with atypia

Tremblay, Breast Journal 2005
Oyama, Virchows 1999
Schnitt, Breast Cancer Research 2003
Dessauvagie Human Path 2007
Aguilar Virchows 2005
Noel Virchows 2006
Simpson, AJSP 2005
Premenopausal

Postmenopausal

Low Grade DCIS

Also: normal breast in BrCa have higher ER

Usual Hyperplasia
Flat Epithelial Atypia

Separation of atypical columnar cell lesions (FEA) from non-atypical columnar cell lesions is important in immediate management decisions (ie excision or no excision after core needle biopsy)
Not a good marker to differentiate CCC/CCH vs FEA
Interobserver agreement in diagnosis of FEA

• Seven pathologist → power point tutorial
• Images of 30 columnar cell lesions: FEA / No atypia
• Multi-rater kappa value: 0.83
• However
  – All with interest in breast pathology
  – Images rather than real slides used

** Correct diagnosis / agreement on “Atypia” is important since it may make the difference between excision and no excision

O’Malley, Mod Path 2006
Clinical Significance

More frequently seen nowadays because of mammographic screening (Ca^{++}).

Fraser, AJSP 1998
Clinical Significance

Often seen in association with

– Tubular carcinoma
– ADH
– DCIS
– Lobular neoplasia (ALH/LCIS).

Liebl, Histopathology 2007
Abdel-Fatah, AJSP 2007
Bratthauer, Virchows 2004
Goldstain, AJCP 1996
Genetic Abnormalities in FEA

PCR done for Loss of Heterozygosity (LOH) (2p, 3p, 11q, 16q, 17q)

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>LOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat Lesions (n:22)</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Monomorphic (FEA) (n:13)</td>
<td>9 (70%)</td>
</tr>
<tr>
<td>Polymorphic (n:9)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Tubular Carcinoma (n:10)</td>
<td>9 (90%)</td>
</tr>
</tbody>
</table>

Tubular Carcinoma and Flat lesions shared common LOH pattern (at least 1 locus) in 70% of the cases

Moinfar, Cancer 2000
Flat Epithelial Atypia

Synonyms

- Columnar alterations with prominent, apical snouts and secretions (CAPSS) with atypia
- Columnar cell change with atypia
- Columnar cell hyperplasia with atypia
- Clinging carcinoma, monomorphic type
- DIN 1A, flat monomorphic type
- Atypical cystic duct
- Atypical cystic lobules
- Atypical lobules type A
- Hypersecretory hyperplasia with atypia
- Pretubular hyperplasia
Flat Epithelial Atypia

Association with other lesions

• “Atypical cystic lobules” found more common in specimens with DCIS, than in specimens without DCIS (36% versus 3%) also there was geographic proximity between these lesions (Oyama et. al.).

• Association between “small ectatic ducts lined by atypical cells with apocrine snouts” with both low grade DCIS and tubular carcinoma (Goldstein et. al).

• Various associations found between “flat atypical lesions” and DCIS and/or invasive carcinoma (Page et.al, Rosen et. al).

• Weidner noted similarity between “small ectatic ducts lined by one or two layers of columnar cells with apical snouts” and tubular carcinoma and he considered these as low grade DCIS.

Flat Epithelial Atypia

Association with other lesions

- FEA seen in 48% of the tubular carcinoma vs 13% of Grade 1 invasive ductal carcinoma

- Lobular neoplasia coexisted in 86% with FEA.

- “Atypical Cystic Lesions” seen
  - In breast bx with LN: 56%
  - In 60% of cases with LCIS
  - In 46% of cases with ALH

- “Columnar Cell Lesions” seen in association with
  - ADH in 60% of cases
  - Low grade DCIS in 42% cases

- In 543 DCIS, FEA is significantly associated with
  - Low nuclear grade DCIS, micropapillary and cribriform architecture
**Flat Epithelial Atypia**

**Association with other lesions**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Invasive carcinoma</th>
<th>Lobular carcinoma (% of invasive carcinoma)</th>
<th>LIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk DIN (UDH) n=426</td>
<td>10 (2%)</td>
<td>1 (10%)</td>
<td>43 (10%)</td>
</tr>
<tr>
<td>DIN 1-flat type (Flat epithelial atypia) n=1000</td>
<td>68 (7%)</td>
<td>19 (28%)</td>
<td>257 (26%)</td>
</tr>
<tr>
<td>(ADH/DCIS G1) n=538</td>
<td>116 (22%)</td>
<td>11 (9%)</td>
<td></td>
</tr>
<tr>
<td>DIN 2 (DCIS G2) n=383</td>
<td>142 (37%)</td>
<td>11 (8%)</td>
<td></td>
</tr>
<tr>
<td>DIN 3 (DCIS G3) n=281</td>
<td>102 (36%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

*Bratthauer et al Virchows 2004*
Flat Epithelial Atypia
Association with other lesions

- **“Rosen Triad”:** tubular ca + LCIS + “Columnar cell lesion” (includes non-atypical lesions)
  - All of 86 TC had CLL 79% of which were atypical (i.e. FEA)
  - 53% had all three i.e TC, LCIS, CCL
- Core biopsies done for calcifications: 54% of the LN was associated with “Columnar cell alteration” (includes non-atypical lesions).
  - 9.6% LN→ upgrade to cancer on excision
  - 13% LN+ CCA→ upgrade to cancer on excision
- 42 / 100 breast bx done for Ca++ had “CAPPs” (includes non-atypical lesions)
  - More commonly associated with low-grade DCIS
FEA in CNB: to excise not to excise

- 37 / 142 (20%) CAPSS (includes non-atypicals) \(\rightarrow\) excised
  - 1 / 6 (16%) CAPSS without atypia on excision \(\rightarrow\) DCIS
  - 4 / 31 (13%) CAPSS with atypia (ie FEA) on excision \(\rightarrow\) 3 DCIS + 1 invasive

- 3 / 12 (25%) pure FEA \(\rightarrow\) cancer on excision
  - FEA coexisted with ADH 73% of the time

- 2 / 9 (22%) “columnar cell lesion with atypia” \(\rightarrow\) cancer

- 1 / 5 (20%) “columnar cell lesion with atypia” \(\rightarrow\) cancer

Guerra-Wallace Am J Surgery 2004
Kunju, Hum Path 2007
Bonnett Mod Path 2003
Lim J Clin Path 2006
Problems with the literature

- Lack of uniform terminology
- Lack of multidisciplinary approach
- Non-atypical and atypical columnar cell lesions analyzed together
- Most series include other, coexistent high risk lesions such as ADH
- No radiologic-pathologic correlation
  - No explanation why some FEA not excised (and in some studies why some non-atypicals are excised)
Morphologic Parameters of FEA as Predictors of Malignancy on Excision

859 VANCB from 14 institutions in Italy with follow up excision

Bianchi et al Virchows Arch 2012
Morphologic Parameters of FEA as Predictors of Malignancy on Excision

<table>
<thead>
<tr>
<th>Mention of FEA at VANC</th>
<th>Diagnosis at surgical excision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign, N</td>
<td>Atypia, N</td>
</tr>
<tr>
<td>Pure FEA</td>
<td>73</td>
<td>99</td>
</tr>
<tr>
<td>FEA + ADH</td>
<td>72</td>
<td>128</td>
</tr>
<tr>
<td>FEA + LIN</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>FEA + ADH + LIN</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>167 (28.4 %)</td>
<td>308 (52.3 %)</td>
</tr>
</tbody>
</table>
Morphologic Parameters of FEA as Predictors of Malignancy on Excision

Pure FEA:

– No association with any variables including extent of FEA, degree of atypia (mild vs moderate), BIRADS category, number of cores

– Trend for mild vs moderate atypia and incomplete removal of microcalcifications

Bianchi et al Virchows Arch 2012
Pure FEA on CNB: Is There a Place for Excision?

3,948 Breast CNB

145 (3.7 %)
Pure FEA
- 46% Calcification
- 66% Excision
- 3.2% Upgrade
- 0.2% Upgrade

58 (1.5%)
FEA and ADH
- 86% Calcification
- 74% Excision
- 18.6% Upgrade
- 13.8% Upgrade

Not all excised, patient decision

Uzoaru et al Virchows Arch 2012
Pure FEA: Is There a Place for Excision?

1,678 CNB (VABB)

52 (3%) Pure FEA
86% Calcification
12% Mass
>90% excised
12% BI-RADS 5
3 (6%) Upgrade
(2/3 BI-RADS 5)
### Table 1  Flat epithelial atypia and co-existing lesions on core biopsy

<table>
<thead>
<tr>
<th>Total</th>
<th>FEA only</th>
<th>ADH</th>
<th>ALH</th>
<th>ADH &amp; ALH</th>
<th>LCIS</th>
<th>DCIS</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>94 (45%)</td>
<td>60 (29%)</td>
<td>19 (9%)</td>
<td>9 (4%)</td>
<td>2 (1%)</td>
<td>14 (7%)</td>
<td>12 (6%)</td>
</tr>
</tbody>
</table>

Calhoun Mod Pathol 2014
FEA on Core Bx: Management may be Individualized

**Table 2** Excision after flat epithelial atypia alone on core biopsy

<table>
<thead>
<tr>
<th>Total</th>
<th>No atypia</th>
<th>FEA</th>
<th>ADH</th>
<th>ALH</th>
<th>DCIS</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>20 (27%)^a</td>
<td>31 (42%)</td>
<td>14 (19%)</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Pure FEA upgrade 7%
No upgrades if all calcifications removed

Calhoun Mod Pathol 2014
Pure FEA on Core Bx: Management may be Individualized

<table>
<thead>
<tr>
<th>Core biopsies</th>
<th>Excisions</th>
<th>Carcinoma (%)</th>
<th>DCIS</th>
<th>Invasive</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavoue et al (^{38})</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerra-Wallace et al (^{21})</td>
<td>39</td>
<td>60</td>
<td>8 (13%) (^{a})</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Bianchi et al (^{27})</td>
<td>190</td>
<td>190</td>
<td>18 (10%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chivukula et al (^{33})</td>
<td>39</td>
<td>35</td>
<td>5 (14%)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Noske et al (^{39})</td>
<td>43</td>
<td>30</td>
<td>2 (7%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Senetta et al (^{40})</td>
<td>41</td>
<td>36</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ceugnart et al (^{41})</td>
<td>63</td>
<td>52</td>
<td>2 (4%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Biggar et al (^{42})</td>
<td>51</td>
<td>51</td>
<td>3 (6%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Khoumais et al (^{43})</td>
<td>104</td>
<td>94</td>
<td>10 (11%)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Uzoaru et al (^{44})</td>
<td>145</td>
<td>95</td>
<td>3 (3%)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Peres et al (^{45})</td>
<td>128</td>
<td>95</td>
<td>9 (10%)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Villa et al (^{46})</td>
<td>142</td>
<td>121</td>
<td>7 (6%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>This study</td>
<td>94</td>
<td>73</td>
<td>5 (7%)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1139</strong></td>
<td><strong>963</strong></td>
<td><strong>76 (8%)</strong></td>
<td><strong>32</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

Studies including 30 or more excisions from 2010-2014

Calhoun Mod Pathol 2014
Epithelial Atypia in Excisional Bx performed for Calcifications: Long term follow up

- 971 of 2,833 (34%) Surgical biopsy done for calcifications had “Epithelial Atypia” (included ADH, FEA, LN).
- 670/971 without accompanying carcinoma
- 101/2,833 (3.5%) of all surgical Bx had FEA
  - 84/101 (83%) of FEA was isolated
  - 17/101 (17%) FEA had concomitant cancer
  - None of the FEA developed subsequent carcinoma (mean follow up 160 months)

De Mascarel et al Virchows 2007
FEA

Risk of progression to cancer is very low when isolated lesion

Current recommendation:

– Not to re-excise if FEA is at the margin of a lumpectomy
– Not include FEA when determining the size of DCIS
Columnar cell lesions without atypia → Columnar cell lesions ATYPICAL / FEA → LG-DCIS → Invasive cancer, low grade

Re-excise if margins positive
To excise or not to excise after core biopsy

Columnar cell lesions without atypia → Columnar cell lesions ATYPICAL / FEA → LG-DCIS → Invasive cancer, low grade
Tamoxifen

Columnar cell lesions without atypia

Columnar cell lesions ATYPICAL / FEA

LG-DCIS

Invasive cancer, low grade

Risk reduction
31% DCIS
56% LCIS
86% Atypical hyperplasias

ER+ cases

ADH

Tamoxifen
Flat Epithelial Atypia

Atypical and non-atypical columnar lesions may be biologically related, may represent spectrum of changes and in future both may be proven to be risk factors for breast cancer requiring similar follow up and treatment.
Lobular Neoplasia (LCIS/ALH)
Lobular Neoplasia (LCIS/ALH)

- Rare lesions 0.5%-3.8% of breast biopsies
- Incidence has been increasing in all ages
  - Hormone replacement therapy (up to 2002)
  - Use of larger gauge needles and VABB
  - Calcifications in 20-25% of LCIS (upto 42% of LCIS in Karabakhtsian et al)
- Multicentric (48%), bilateral (>50%)

Hanby, Histopathology 2008
Collins, Cancer 2007
Lobular Neoplasia (LCIS/ALH)

- Similar (?) risk for ipsilateral and contralateral breast
- The risk of development of breast carcinoma after LCIS is about 1-2% / year with a life-time risk of 30-40% (RR x8-10). RR x4 for ALH
- Nurses Health Study: both ALH and ADH ~60% ipsilateral. ALH in premenopausal women RRx7.3
- Risk of subsequent carcinoma after ALH and/or LCIS is 3 x more likely in ipsilateral breast

Hanby, Histopathology 2008
Collins, Cancer 2007
Page, Lancet 2003
Lobular Neoplasia (LCIS/ALH)

- ALH: partial involvement
- LCIS: >1/2 lobule involved and must be filled and distended (Page: at least 8 cells within its cross sectional diameter)

Difficulties differentiating ALH from LCIS:
- Core biopsy
- Underlying lesion such as sclerosing adenosis
- When only Pagetoid spread is present
Page
*50%
*likes distention
*doesn’t like lumens/spaces in LCIS

Rosen
*75%
*doesn’t care about distention
*OK with lumens/spaces in LCIS
Tavassoli
*residual lumens OK in LIN 2 but Not in LIN 3
Page: ALH because less than 50% distended
Rosen: LCIS because >75% involved
Tavassoli: LIN 2
Lobular Neoplasia (LCIS/ALH)

- Lacks: E-cadherin, ß- and α-catenin
- P120: cytoplasmic staining (rather than membranous staining)
- Poor fixation may mimic discohesion in TDLU (less of a problem in core biopsies)
E-cadherin

- Helpful in difficult cases but should not be the magic tool to differentiate ductal vs lobular neoplasia
- Aberrant E-cadherin staining in 15% ductal and lobular lesions

<table>
<thead>
<tr>
<th>Cases/diagnoses</th>
<th>Complete absence</th>
<th>Weak/partial fragmented</th>
<th>Focal/dot-like cytoplasm</th>
<th>Complete membrane</th>
<th>Reduced/weak membrane</th>
<th>Antibody clone/dilution</th>
<th>IHC staining technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 LN/ILC</td>
<td>121 (86.4%)</td>
<td><strong>16 (11.5%)</strong></td>
<td>3 (2.1%)</td>
<td></td>
<td></td>
<td>ECH-6 clone</td>
<td>HIER</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cell Marque, prediluted</td>
<td>Citrate, pH 6.0</td>
</tr>
<tr>
<td>21 DCIS/IDC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 (71.4%)</td>
<td><strong>6 (28.6%)</strong></td>
<td>EnVision Plus</td>
</tr>
</tbody>
</table>

CIS, carcinoma in situ; DCIS, duct carcinoma in situ; HIER, heat-induced epitope retrieval; IDC, infiltrating duct carcinoma; ILC, infiltrating lobular carcinoma.

Bold number and percentage: cases with aberrant E-cadherin reaction.

- Interobserver variability, variation with the Ab used

Choi et al Mod Path 2008
LCIS

• 1941 Foot and Stewart
  – concluded LCIS is premalignant and recommended mastectomy

• After 3 decades it was noticed that LCIS do not uniformly progress to invasive cancer and risk is bilateral

• In 1978 Haagensen coined the term lobular neoplasia to discourage surgeons from performing mastectomy because of low risk of subsequent breast cancer and that unilateral mastectomy would not address the nearly equal risk of contralateral breast cancer
LCIS

- Many was reluctant to redefine LCIS as purely non-malignant lesion as:
  - LCIS is associated with greater risk for subsequent cancer than is ALH
  - LCIS may be occasionally be direct precursor of invasive lobular cancer (such as same truncating e cadherin mutations seen in invasive locular cancer adjacent to LCIS (Berx et al 1996)
- Nomenclature has not changed the recommendations that LCIS should not be treated with surgery
- 1990s consensus was LCIS is a risk factor but not precursor for BrCa → no further surgical treatment after Bx diagnosis
Is the Management of LCIS the Same as DCIS?

- LCIS in core bx → ??
- LCIS in excisional bx → no further excision
- LCIS at lumpectomy margin → noted but not re-excised
- Post-excision radiotherapy not recommended
- Hormonal therapy recommended

- DCIS on core bx → lumpectomy
- DCIS in excisional biopsy may need re-excision if margins positive
- DCIS at lumpectomy margin → re-excised
- Post lumpectomy radiotherapy required in most cases
- Hormonal therapy recommended in ER+ DCIS
Is the Management of LCIS the Same as DCIS?

- LCIS in core bx → ??
- LCIS in excisional bx → no further excision
- LCIS at lumpectomy margin → noted but not re-excised
- Post-excision radiotherapy not recommended
- Hormonal therapy recommended

- DCIS on core bx → lumpectomy
- DCIS in excisional biopsy may need re-excision if margins positive
- DCIS at lumpectomy margin → re-excised
- Post lumpectomy radiotherapy required in most cases
- Hormonal therapy recommended in ER+ DCIS
Is re-excision needed after LCIS at lumpectomy or excisional biopsy margin?

Did local recurrence vary with co-existing LCIS in women with breast cancer

### TABLE 3
Comparison of Reports with LCIS as a Component of Breast Carcinoma Treated with BCS and RT

<table>
<thead>
<tr>
<th>Reporting institution</th>
<th>Stage of disease</th>
<th>No. of control patients</th>
<th>No. of patients with LCIS</th>
<th>Median follow-up in mos</th>
<th>Risk of local failure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox Chase(^{21})</td>
<td>I-II</td>
<td>1209</td>
<td>65</td>
<td>76</td>
<td>5%</td>
<td>3% After 5 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29%</td>
<td>6% After 10 yr</td>
</tr>
<tr>
<td>Yale(^{22})</td>
<td>0-II</td>
<td>1045</td>
<td>51</td>
<td>127</td>
<td>23%</td>
<td>16%</td>
</tr>
<tr>
<td>Harvard(^{23})</td>
<td>I-II</td>
<td>1062</td>
<td>137</td>
<td>161</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>University of Michigan (current study)</td>
<td>0-II</td>
<td>121 matched</td>
<td>64</td>
<td>45</td>
<td>1.7%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

LCIS: lobular carcinoma in situ; BCS: breast-conserving surgery; RT: radiotherapy; +LCIS: with lobular carcinoma in situ; −LCIS: without lobular carcinoma in situ; NS: not significant.

Ben-David et al Cancer 2006
Is re-excision needed after LCIS at margin?

Extent of LCIS or its presence at the margins did not effect excellent local control with breast conserving surgery and RT.
Lobular Neoplasia
To Excise or Not to Excise After Core Needle Biopsy
NCCN / LCIS

DIAGNOSIS

- Lobular carcinoma in situ (LCIS) identified on breast biopsy
  - T0, N0, M0

  - History and physical
  - Diagnostic bilateral mammogram
  - Pathology review

  - Initial biopsy was surgical biopsy

WORKUP

- Perform surgical excision

RISK REDUCTION

- LCIS without other cancer

- Counseling regarding risk reduction, see NCCN Guidelines for Breast Cancer Risk Reduction

SURVEILLANCE

- Surveillance as per
  - NCCN Guidelines for Breast Cancer Risk Reduction
  - NCCN Guidelines for Breast Cancer Screening and Diagnosis

- Ductal carcinoma in situ (DCIS)

  - See NCCN Guidelines for DCIS (DCIS-1)

- Invasive breast cancer

  - See NCCN Guidelines for Invasive Breast Cancer (BINV-1)

Notes:

- Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.
Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.

Therefore, according to the NCCN Panel, it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude an associated invasive cancer or DCIS. More than 4 foci of LCIS may also increase the risk for upstaging on surgical biopsy. The NCCN Panel recommends that LCIS of the usual type (involving <4 terminal ductal lobular units in a single core) found on core biopsy, as a result of routine screening for calcifications and without imaging discordance, may be managed by imaging follow-up.
Morphologic Parameters of LN as Predictors of Malignancy on Excision

<table>
<thead>
<tr>
<th>LN, pure or associated with other lesions at VANC</th>
<th>Benign, no.</th>
<th>Atypia/LCIS, no.</th>
<th>Malignancy</th>
<th>Total, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure LN (ALH + LCIS)</td>
<td>25</td>
<td>99</td>
<td>25*</td>
<td>149 (52.1)</td>
</tr>
<tr>
<td>Pure ALH</td>
<td>18</td>
<td>59</td>
<td>13</td>
<td>90 (31.5)</td>
</tr>
<tr>
<td>Pure LCIS</td>
<td>7</td>
<td>40</td>
<td>12</td>
<td>59 (20.6)</td>
</tr>
</tbody>
</table>

Bianchi et al Histopathology 2013
Morphologic Parameters of LN as Predictors of Malignancy on Excision

– Significant association with BiRADS 4-5
– NO association with extent of LN

Bianchi et al Virchows Arch 2012
Recommendations for Excision

- Despite removal of calcifications some cases may still have cancer on excision
- Unable to identify particular mammographic, technical findings or features that would indicate LN more likely to be upgraded

Elsheikh, AJCP 2002
Foster, Radiology 2004
Mahoney, AJR 2006
Dr Rodman: “Any attempt to make the diagnosis more exact is certainly praiseworthy. Being a surgeon, however, I am not sure but that sometimes x-ray men have somewhat vivid imaginations. The clinical diagnosis of carcinoma of the breast and chronic cystic mastitis is not ordinarily difficult, and therefore until we have x-ray evidence of a more positive value we had best go a little slow in accepting evidence which is contrary to clinical findings”
# Findings at Surgical Excision of LN

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases With Follow-Up Excision</th>
<th>Findings at CNB</th>
<th>Findings at EXB</th>
<th>Comments on Cases With Upgrade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALH</td>
<td>LCIS</td>
<td>LN</td>
<td>No</td>
</tr>
<tr>
<td>Shin &amp; Rosen, 2002&lt;sup&gt;7b&lt;/sup&gt;</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Middleton, 2003&lt;sup&gt;8b&lt;/sup&gt;</td>
<td>17</td>
<td>6</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Renshaw, 2006&lt;sup&gt;30b&lt;/sup&gt;</td>
<td>92</td>
<td>NA</td>
<td>NA</td>
<td>92</td>
</tr>
<tr>
<td>Cangiarella, 2008&lt;sup&gt;29b&lt;/sup&gt;</td>
<td>38</td>
<td>18</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Elsheikh &amp; Silverman, 2005&lt;sup&gt;22c&lt;/sup&gt;</td>
<td>33</td>
<td>20</td>
<td>13</td>
<td>NA</td>
</tr>
<tr>
<td>Liberman, 1999&lt;sup&gt;6b&lt;/sup&gt;</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Hwang, 2006&lt;sup&gt;21b&lt;/sup&gt;</td>
<td>87</td>
<td>48</td>
<td>39</td>
<td>NA</td>
</tr>
<tr>
<td>Nagi, 2008&lt;sup&gt;20b&lt;/sup&gt;</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
<td>45</td>
</tr>
<tr>
<td>Rendi, 2011&lt;sup&gt;27c&lt;/sup&gt;</td>
<td>68</td>
<td>20</td>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Current study&lt;sup&gt;2&lt;/sup&gt;</td>
<td>72</td>
<td>42</td>
<td>30</td>
<td>NA</td>
</tr>
</tbody>
</table>

Murray Cancer 2013
Lobular Neoplasia
Outcomes of Prospective Excision

All pure LN excised (n=80)
  – 72/80 (90%) → concordant Rad-Path
    • 2/72 (3%) upgrade
      Calcs in benign glands
  – 8/80 (10%) → discordant Rad-Path
    • 3/8 (38%) upgrade
      Upgrades: insufficient explanation for mass

Murray et al  Cancer 2013
Multidisciplinary approach LN

- Retrospective study with long f/u
- 124 LN
- 104 patients were clinically and or radiologically monitored
- Median follow up 3.4 years (range: 0.44-8.6 years)
# Multidisciplinary approach LN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Levels</th>
<th>Yes (n = 8)</th>
<th>No (n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal (&lt;3 TDLU) vs. extensive ≥3 TDLU</td>
<td>Extensive Focal</td>
<td>8 (32%)</td>
<td>17 (68%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Targeted vs. incidental</td>
<td>Incidental Targeted</td>
<td>1 (1.6%)</td>
<td>61 (98.4%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Percentage of lesion removed during biopsy</td>
<td>&lt;Half excised</td>
<td>7 (25.9%)</td>
<td>20 (74.1%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;Half excised</td>
<td>2 (5.6%)</td>
<td>34 (94.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Middleton, Cancer Medicine 2012
BIRADS Breast Imaging Reporting and Data System

0: Incomplete
1: Negative
2: Benign finding(s)
3: Probably benign (≤2% risk of malignancy)
4: Suspicious abnormality
5: Highly suggestive of malignancy
6: Known biopsy – proven malignancy
Major goal of CNB is to reduce number of open surgical biopsies. As such the threshold for proceeding to open biopsy should be relatively low particularly in the absence of firm data on which to base management decisions.
Recommendations for Excision

- Co-existing high-risk lesions such as ADH
- Morphologic overlap with DCIS
- Mixed E-cadherin staining
- Pleomorphic LCIS
- Radiologic-pathologic discordance
- Mass or architectural distortion
- Calcifications associated with LN
- h/o breast cancer
- Necrosis
- “Extensive” LN

Pinder Pathology 2007
Reynolds AJR 2000
Reis-Filho JCP 2006
Karabakhtsian, AJSP 2007
Shin, Arch Path 2002
Cangieralla, Arch Path 2008
Pleomorphic LCIS (PLCIS)

- Large, pleomorphic, discohesive cells with eccentric nuclei and eosinophilic cytoplasm
- Comedo necrosis is common and makes it difficult to differentiate from high-grade DCIS
- E-cadherin negative, cytoplasmic p120 catenin +, GCDFP15 +
- PLCIS found more commonly with invasive lobular cancer compared to usual LCIS about 45% of the time, especially pleomorphic invasive lobular carcinoma

Chivukala et al. AJSP 2008
Dabbs et al Appl Immuno 2007
Middleton et al AJSP 2000
Pleomorphic LCIS

- 12 PLCIS in core biopsy $\rightarrow$ excised
  - 10/12 (83%) residual PLCIS
  - 3/12 (25%) invasive lobular carcinoma
- 11/12 (92%) ER + ; 6/12 (50%) PR +
- 3/12 (25%) HER2 +
- High Ki-67 staining in 11/12 cases

Chivukala et al. AJSP 2008
PLCIS

- 6/26 PLCIS with positive margin
- 1/26 (3.8%) locally recurred at 19 months similar to recurrence rates after DCIS

Downs-Kelly et al Arch Pathol 2011
What is the biological relationship between “incidental” lesions and high risk lesions?
Association between LN and FEA

- 80% of the 111 breast biopsy specimens which contained LN (excluded DCIS and invasive cancer) had FEA
- 42% of LN and ADH also harbored FEA

Leibl et al Histopathology 2007
Bratthauer et al Virchows 2004
Stem cell(s)

Low Nuclear Grade Breast Neoplasia
*Columnar cell lesions/FEA
*ADH/low grade DCIS
*LN
*Invasive tubular, lobular and tubulo-lobular carcinoma

High Nuclear Grade Breast Neoplasia
<table>
<thead>
<tr>
<th><strong>Low Nuclear Grade</strong></th>
<th><strong>High Nuclear Grade</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diploid/near diploid</td>
<td>Aneuploid</td>
</tr>
<tr>
<td>Recurrent loss of 16q</td>
<td>Complex genetic profiles</td>
</tr>
<tr>
<td>Gains of 1q</td>
<td>Infrequent deletion of 16q</td>
</tr>
<tr>
<td>Negative basal and myoepithelial markers</td>
<td>More likely to be positive for basal, myoepithelial markers</td>
</tr>
<tr>
<td>Positive CK19/18/8</td>
<td>More likely to be triple negative</td>
</tr>
<tr>
<td>Positive ER, bcl-2, cyclinD1</td>
<td></td>
</tr>
</tbody>
</table>

Abdel-Fatah et al AJSP 2008
Abdel-Fatah et al AJSP 2007
Low Grade Pathway

Chromosome 16q loss:

FEA
ADH
LN
LG-DCIS

Quantitative & Temporal expression of genes

Low Grade Invasive Carcinoma

UDH = Random chromosome alterations similar to normal breast
Excision Recommended after ADH Diagnosed in MRI or US Guided Bx
ADH in VAB of Breast Microcalcifications

140 ADH VABB

EXCISION (n= 121)
Upgrade 16 (13%)
Ass’ed with:
  > 2 TDLU
  removal of <95% calcs

FOLLOW UP (n= 19)
No new lesions

Nguyen Ann Surg Oncol 2011
Benign Solitary Intraductal Papillomas

• Close imaging follow up unless
  – Discordance between imaging and pathology
  – Papillary lesion associated with mass
Thank you