Long term follow-up of patients with indeterminate breast (B3) lesions

A 10-year prospective review

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Introduction

What are indeterminate or B3 breast lesions?

Family of breast lesions including a variety of pathologies

- papilloma
- radial scars
- atypical ductal hyperplasia (ADH/AIDEP)
- flat epithelial atypia (FEA)
- lobular neoplasia (LN)
- fibroepithelial lesions (FEL)
- miscellaneous lesions such as mucoceles, spindle cell lesions etc.

Mostly screen detected

- around 8% of all biopsies in the UK breast screening program

Breast core biopsy grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Normal breast tissue</td>
</tr>
<tr>
<td>B2</td>
<td>Benign lesion</td>
</tr>
<tr>
<td>B3</td>
<td>Lesions of uncertain malignant potential</td>
</tr>
<tr>
<td>B4</td>
<td>Suspicious of malignancy</td>
</tr>
<tr>
<td>B5</td>
<td>Malignant lesion</td>
</tr>
<tr>
<td>B5a</td>
<td>Malignant, in situ</td>
</tr>
<tr>
<td>B5b</td>
<td>Malignant, invasive</td>
</tr>
<tr>
<td>B5c</td>
<td>Malignant, invasive status not assessable</td>
</tr>
</tbody>
</table>
Association with malignancy

B3 breast lesions are not malignant per se, but are associated with malignancy

The association with malignancy may be either:

• At the time of diagnosis
• As a risk factor for future malignancy

At diagnostic core biopsy, malignancy might not be identified due to:

• Lesion Heterogeneity (A)
• Pathological Underestimation (B)

Risk factor for future malignancy:

• Varies between studies and lesions
• As much as 5-fold in some published studies

A: Malignant areas (purple) within a mass (e.g. papilloma with atypia) where the core samples the lesion, but does not include the malignant areas

B: With a small gauge biopsy the number of abnormal areas (purple dots) can be too few to reach a diagnostic threshold (e.g. for DCIS). In a larger biopsy, a greater number of abnormal areas are sampled in a single core reducing the risk of under-sampling error.
Background

Moving from surgical excision to VAE

To manage the risk of under sampling error, historically, all B3 lesions underwent diagnostic surgical excision.

The risk of malignancy varies between lesions, but the majority (>70%) of lesions remain benign following surgery.

Various publications advocate replacing surgery with second line vacuum assisted excision biopsy (VAE) with 7/8 G needles to

- Improve preoperative cancer diagnosis
- Reduce unnecessary benign surgery

Guidelines\(^5,6,7\) suggest that this is followed with

- 5 yearly mammography follow-up of atypical lesions
- Routine screening for non atypia lesions

Limited evidence for lesions managed this way is published

This is a long-term prospective study of women after B3 diagnosis

- Is VAE is a safe alternative to surgery?
- Are surveillance strategies appropriate?

### Needle gauge

<table>
<thead>
<tr>
<th>Needle gauge</th>
<th>Outer diameter (inches)</th>
<th>Outer diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.180</td>
<td>4.572</td>
</tr>
<tr>
<td>10</td>
<td>0.134</td>
<td>3.404</td>
</tr>
<tr>
<td>14</td>
<td>0.083</td>
<td>2.108</td>
</tr>
</tbody>
</table>
Methods

Prospective single centre follow up study

All B3 lesions with no previous or concurrent malignancy identified January 2012 to December 2016

All lesions were managed with VAE pathways as appropriate following multidisciplinary team review

Any lesions upgraded to carcinoma by VAE were managed as appropriate

The remaining women were followed up for any subsequent breast cancer diagnosis

The rate of cancer development in the B3 group was compared to a group of women with benign screen-detected lesions identified in 2012 which were assessed and then returned to routine recall in the NHS Breast Screening Program

Follow up for both groups was until December 2021

Simplified management flow chart

- Calcs
- Mass
- 10G or 14G biopsy
- B3 result
- 7G or 8G large volume biopsy if suitable
  - No atypia
    - Routine recall or discharge
  - Atypia, no malignancy
    - 5 years annual screening mammogram
  - Malignant
    - Therapeutic surgery

Lesions unsuitable for VAE
- Lesion type (not papilloma with atypia, some miscellaneous lesions)
- Patient choice
- Technically impossible
## Results

### 514 B3 lesions identified over 5 years

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number</th>
<th>2nd line VAE</th>
<th>B5b</th>
<th>B5a</th>
<th>B4</th>
<th>B3</th>
<th>B2</th>
<th>B1</th>
<th>B5 @ diag ex</th>
<th>No Upgraded (%)</th>
<th>Number on surveillance</th>
<th>No with subsequent B5 diagnosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDEP</td>
<td>110 (21.4%)</td>
<td>87</td>
<td>2</td>
<td>14</td>
<td>1</td>
<td>35</td>
<td>33</td>
<td>2</td>
<td>7</td>
<td>23</td>
<td>87</td>
<td>10 + lymphoma (12.6%)</td>
</tr>
<tr>
<td>Atypical FA/FELs</td>
<td>14 (2.7%)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>13</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>FEA</td>
<td>43 (8.4%)</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>17</td>
<td>18</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>39</td>
<td>2 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>LISN</td>
<td>94 (18.3%)</td>
<td>62</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>35</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>12</td>
<td>82</td>
<td>(8.5%)</td>
</tr>
<tr>
<td>Pap without atypia</td>
<td>104 (20.2%)</td>
<td>86</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>60</td>
<td>18</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>101</td>
<td>8 (7.9%)</td>
</tr>
<tr>
<td>Pap with atypia</td>
<td>8 (1.6%)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>RS without atypia</td>
<td>93 (18.1%)</td>
<td>74</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>51</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>91</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>RS with atypia</td>
<td>21 (4.1%)</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>18</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>27 (5.3%)</td>
<td>20</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>24</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Totals</td>
<td>514</td>
<td>391</td>
<td>6</td>
<td>30</td>
<td>8</td>
<td>217</td>
<td>117</td>
<td>13</td>
<td>18</td>
<td>54 (10.5%)</td>
<td>460</td>
<td>33 (7.2%)</td>
</tr>
</tbody>
</table>

### 514 B3 lesions
- 391 were suitable for VAE
- 36 (9.2%) upgraded to B5 by VAE
- 18 upgraded following diagnostic excision
- Overall upgrade to carcinoma 10.5%

Remaining 460 patients were offered surveillance mammography
- mean of 3.4 mammograms per patient (range 0-8)
- 44 no further mammograms (age/personal choice)
- 14 deaths (1 breast cancer)
Results

No significant difference between rate of subsequent cancer between B3 lesions or controls at 5 years was observed

In the B3 lesion group
- 33 women (7.2%) developed breast cancer
  - 24 invasive
  - 9 in situ
  - 1 lymphoma

- Median time-to-diagnosis 4 years (range 1-11 years)
- 23/33 identified by mammography
- 10/33 cancers at the site of the initial B3 lesion
- No difference in rate of cancer was identified
  - between subtypes of B3 lesions
  - between lesions managed by VAE vs no VAE
  - between lesions with or without atypia

In the benign control group
- 147 women had benign lesions identified at screening during 2012 (B2/C2 pathology)
- 8 (5.5%) subsequently developed cancer

Cancers per year diagnosed following B3 lesion

Cancer-free survival estimates
**Conclusions**

This study demonstrates that B3 management with VAE is safe and effective

- 7.2% of women with prior B3 lesions subsequently develop breast cancer.

- However, the risk of breast cancer following diagnosis of a B3 lesion is not increased in comparison to a group of women with previously identified screen detected benign lesions.

- No subgroup of B3 lesions was shown to have an elevated risk of subsequent carcinoma. Rate of subsequent carcinoma did not differ between lesions with or without atypia or those managed with or without VAE.

- Cancers post B3 diagnosis occurred at a wide range of time points following a B3 diagnosis and were mammographically detected in two thirds of cases.

- Cancers were often unrelated to the initial B3 lesion, seen at the original B3 site in only one third of cases.

- However, enhanced surveillance strategies post VAE do not offer additional cancer detection than usual screening.

- A safe follow-up strategy of indeterminate breast lesions could comprise a mammographic review at one year followed by return to routine breast screening.
Management Pathway used in Newcastle MDT

Several management guidelines exist. However, this flowchart combines all the individual lesion pathways published, meaning you only need one flowchart at the MDT.