Indeterminate breast lesions

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King's College Hospital, London
Definition

‘breast lesions for which there is uncertainty about the diagnosis, management or natural history’
Indeterminate breast lesions

- clinical
- imaging
- needle biopsy

- natural history
- treatment
Indeterminate breast lesions

clinical

• more referrals to diagnostic clinics with benign changes and minimal signs

• 6 - 8% new referrals have breast cancer

• clinical assessment difficult
**Symptomatic breast cancer clinical assessment**  
\( n = 1139/20,367 \) (5.6\%)  
2000 – 2012

<table>
<thead>
<tr>
<th>Clinical score</th>
<th>&lt; 50 years</th>
<th>&gt;= 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 461</td>
<td>N = 678</td>
</tr>
<tr>
<td>1</td>
<td>5.8</td>
<td>5.1</td>
</tr>
<tr>
<td>2</td>
<td>39.7</td>
<td>17.6</td>
</tr>
<tr>
<td>3</td>
<td>37.1</td>
<td>17.6</td>
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<tr>
<td>4</td>
<td>17.3</td>
<td>21.5</td>
</tr>
<tr>
<td>5</td>
<td>15.4</td>
<td>38.2</td>
</tr>
</tbody>
</table>

KCH Breast Unit Database
Indeterminate breast lesions

imaging

• improvements in imaging FFDM, US, MRI
• more women attending for screening
• more subtle/indeterminate lesions
## Indeterminate lesions - imaging

**B3  \( n = 444 \)**

<table>
<thead>
<tr>
<th>sign</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>microcalcification</td>
<td>203</td>
<td>45.7</td>
</tr>
<tr>
<td>mass</td>
<td>119</td>
<td>26.8</td>
</tr>
<tr>
<td>mass + mcns</td>
<td>53</td>
<td>11.9</td>
</tr>
<tr>
<td>distortion</td>
<td>53</td>
<td>11.9</td>
</tr>
<tr>
<td>asymmetry</td>
<td>8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Lynes K et al, Breast Cancer Res 2011, 13 suppl 1*
Indeterminate breast lesions

**imaging**

- complete imaging work up prior to biopsy

- mammography +/- ultrasound

- MRI not required in primary work up for most cases
Soft tissue lesions –
localised compression/mag
Tomosynthesis
USS
microcalcification - magnification views
Indeterminate breast lesions

**needle biopsy**

- core biopsy and VACB preferred

- aim to diagnose benign or malignant disease

- increased use of CB/VACB has improved preoperative diagnosis of malignancy

*NHSBSP non op diagnosis of cancer 2009/2010

1\textsuperscript{st} screen = 83\%
Inc screen = 89\%
 target 80\%
Indeterminate core biopsy  B3/B4 frequency

- SELBSP  2000 – 2010
  patients  = 5324  14G/VACB
  B3 = 444  (8.3%)  B4 = 38  (0.8%)

  Lynes K et al, Breast Cancer Res 2011, 13 suppl 1

- previous studies
  B3 = 5 – 9%
  B4 = 0.8%

  Rakha E et al  Int J Cancer 2011:129
  Rakha E et al  Histopathology 2011:58
Pathological findings from B3 NCBs

- AIEP: 34%
- Complex sclerosing lesion / radial scar: 22%
- Lobular: 7%
- Phyllodes: 2%
- Mixed: 9%
- Others: 5%
- Papillary: 19%

Lynes K et al, Breast Cancer Res 2011, 13 suppl 1
Indeterminate core biopsy  B3/B4

- outcome

• B3  - 25% malignant
  invasive  - 28%
  DCIS   - 72%

but PPV varies considerably with histology subtype

• B4  - 74% malignant
  invasive  - 39%
  DCIS   - 61%
## PPV of B3 CNB

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>papillary</td>
<td>14</td>
<td>22.7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* 36</td>
</tr>
<tr>
<td>AIEP</td>
<td>35</td>
<td>44</td>
<td>32</td>
</tr>
<tr>
<td>Lobular neoplasia</td>
<td>47</td>
<td>60.9</td>
<td>30</td>
</tr>
<tr>
<td>CSL</td>
<td>6</td>
<td>16.7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* 24</td>
</tr>
<tr>
<td>N =</td>
<td>444</td>
<td>372</td>
<td>523</td>
</tr>
</tbody>
</table>

1. Lynes K et al, Breast Cancer Res 2011, 13 suppl 1
2. Houssami N et al, BJC 2007 96, 1253-1257
Indeterminate breast lesions

- benign surgical biopsy should be minimised for screen detected lesions

London Region 2008/2009

275 women – diagnostic surgery

benign – 193  malignant – 82

- need to ensure that significant lesions are not underdiagnosed and that low risk lesions are not overtreated
‘The management of indeterminate breast lesions – a clinicians guide’

guideline developed by a London region multidisciplinary team

Patients who have undergone breast needle biopsy should be discussed at a multidisciplinary meeting to decide on management
Papillary lesions
### A – pathology CB/VAC corresponds to mammographic lesion

**Papilloma**

<table>
<thead>
<tr>
<th></th>
<th>Non operative</th>
<th>Follow up</th>
<th>Operative</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solitary papilloma</strong></td>
<td><em>VAC to remove lesion (no atypia)</em></td>
<td>none</td>
<td><em>Local excision, fully excised</em></td>
<td>none</td>
</tr>
<tr>
<td><strong>Multiple peripheral papillomas</strong></td>
<td><strong>Diagnostic VAC of index lesion</strong></td>
<td><strong>Standard increased risk surveillance</strong></td>
<td><strong>Remove lesion (consider risk reducing surgery)</strong></td>
<td><strong>Standard increased risk surveillance</strong></td>
</tr>
</tbody>
</table>

* preferred method
epithelial atypia
CN  Microcalcification  CC Mag  Lat Mag
A – pathology *CB/VAC* corresponds to mammographic lesion atypical ductal proliferation

<table>
<thead>
<tr>
<th>Atypical ductal proliferation</th>
<th>Non operative</th>
<th>Follow up</th>
<th>Operative</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1cm mcns</td>
<td>VAC – if lesion fully removed and no DCIS Consider repeat VAC</td>
<td>Standard increased risk surveillance</td>
<td>* Excision of mammo lesion/marker</td>
<td>Standard increased risk surveillance</td>
</tr>
</tbody>
</table>

| Extensive mcns with ADH on initial biopsy | VAC of more than one area | If no DCIS, refer for diagnostic excision | Diagnostic biopsy of most suspicious area | Atypia only – Standard increased risk surveillance |

* preferred method
In situ lobular neoplasia

LCIS  > 50% acini in lobule filled with malignant cells

ALH  < 50%
$e$ cadherin negative for lobular neoplasia

DCIS $e$ cadherin +ve
### A – pathology CB/VAC corresponds to mammographic lesion lobular neoplasia

<table>
<thead>
<tr>
<th></th>
<th>Non operative</th>
<th>Follow up</th>
<th>Operative</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lobular neoplasia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT pleomorphic LCIS or LCIS with necrosis</td>
<td>Assess mammography abnormality</td>
<td>Standard increased risk surveillance</td>
<td>*Excise mammography lesion</td>
<td>Standard increased risk surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* preferred method
CSL myoepithelial cells present
**A – pathology CB/VAC corresponds to mammographic lesion**

**Radial scar**

<table>
<thead>
<tr>
<th></th>
<th>Non operative</th>
<th>Follow up</th>
<th>Operative</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial scar &lt; 2cm</td>
<td>*VAC at least 12 samples</td>
<td>none</td>
<td><strong>MDM may elect to recommend excision for lesion &gt; 2cm</strong></td>
<td>None if no atypia</td>
</tr>
<tr>
<td></td>
<td><strong>Excision if atypia</strong></td>
<td></td>
<td></td>
<td><strong>Standard increased risk surveillance if atypia</strong></td>
</tr>
</tbody>
</table>

* preferred method
Management of indeterminate lesions where the pathology is incidental and not predicted by the imaging

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Non Operative</th>
<th>Follow up</th>
<th>Operative</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary papilloma</td>
<td>*VAC</td>
<td>none</td>
<td>Local excision</td>
<td>none</td>
</tr>
<tr>
<td>Multiple papillomas</td>
<td>VAC of index lesion</td>
<td>Standard increased risk surveillance</td>
<td>Excision Consider prophylactic surgery</td>
<td>Standard increased risk surveillance</td>
</tr>
<tr>
<td>Radial scar</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Atypical ductal proliferation</td>
<td>VAC</td>
<td>Standard increased risk surveillance</td>
<td>* Surgical excision if severe atypia</td>
<td>Standard increased risk surveillance</td>
</tr>
<tr>
<td>Lobular neoplasia (non pleomorphic)</td>
<td>VAC if indicated by imaging</td>
<td>Standard increased risk surveillance</td>
<td>? Surgical excision if indicated by imaging</td>
<td>Standard increased risk surveillance</td>
</tr>
</tbody>
</table>
Indeterminate breast lesions

- VACB is the sampling method of choice for lesions often associated with an indeterminate diagnosis
  - radial distortion
  - microcalcification M3

- VACB may also be considered for further sampling of some lesions after an initial B3 diagnosis – confirm atypia or upgrade to DCIS
• A practical guideline has been developed for management of indeterminate lesions diagnosed on CB/VACB

• All such cases should be discussed prospectively at a multidisciplinary meeting

• Further study of the role of VACB in management of intraductal epithelial atypia needed
DCIS

- more known about pathology and biology
- uncertainty about natural history and optimum treatment

Key research questions

1. How can we identify women with low risk disease who do not need treatment and those at high risk who need maximal treatment?

2. Can genotyping help predict risk of progression to invasive disease?

The Low Risk DCIS Trial

Can patients with newly diagnosed low-grade DCIS safely avoid surgery, without detriment to their psychological well-being and can those patients who require surgery be identified by pathological and radiological criteria?

Background

The natural history of asymptomatic and screen-detected ductal carcinoma in situ (DCIS) is not fully understood but it is increasingly being recognised that in some cases the condition will not progress to invasive cancer during the lifetime of a woman diagnosed with this condition. This leads to the concept that breast screening results in ‘overtreatment’ for many women attending for breast screening and has been the subject of much discussion in the professional press and considerable exposure in the lay press. The debate extends into the utility of treating small invasive screen-detected cancers but here we are concerned exclusively with pre-invasive disease. DCIS has traditionally been regarded as a serious condition that should always be treated by complete surgical excision and this frequently requires a mastectomy if the disease is widespread. The paradigms developed for management of symptomatic DCIS have been directly applied to screen-detected and chance finding of DCIS. The proposed trial challenges this paradigm and is intended to establish the safety of leaving certain types of screen-detected DCIS untreated at diagnosis with surgical intervention only used when there is evidence of radiological or histological evidence of disease progression either into overt invasive disease or where radiological progression is sufficient to require surgical excision to exclude or confirm development of invasive cancer.

Trial proposal

The trial proposal is to randomise women with screen-detected (or asymptomatic) low risk DCIS to either conventional surgery or to Active Monitoring. The primary endpoint is the development of ipsilateral invasive breast cancer.

Inclusion Criteria

- Female, age ≥ 46 years
- Screen-detected or incidental microcalcification
- Low risk DCIS on large volume VAB, confirmed by central pathology review
- Patient fit to undergo surgery/attend for annual mammograms, with no concomitant medical, psychiatric or social problems that might prevent follow-up or completion of quality of life (QoL) questionnaires
- No previous breast cancer or DCIS diagnosis
- Written informed consent

Design

This is a non-inferiority trial with a sample size of 932, with a 1:1 randomisation to; A) Standard Treatment with surgery and additional adjuvant treatment according to institutional standard practice followed by annual mammographic follow up or B) Active Monitoring with annual mammograms with re-biopsy and intervention according to pre-specified radiological criteria, such as the development of a mass lesion suggesting the development of invasive disease. After re-biopsy, surgery will only be mandated if the grade of DCIS changes to higher grade or invasive disease.
The Low Risk DCIS Trial

Can patients with newly diagnosed low-grade DCIS safely avoid surgery, without detriment to their psychological well-being and can those patients who require surgery be identified by pathological and radiological criteria?
Conclusions

- triple diagnosis enables a definite diagnosis to be made for 90-95% breast lesions
- use of new sampling technology decreases the need for diagnostic surgery
- further research is needed to decide on optimum management of low risk malignant lesions
Thank you
<table>
<thead>
<tr>
<th>B3 Core biopsy findings</th>
<th>Malignant</th>
<th>Other findings</th>
<th>Predictive value of B3 histology to diagnose malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In situ</td>
<td>Benign</td>
<td>Not excised</td>
</tr>
<tr>
<td>Papillary</td>
<td>8</td>
<td>4</td>
<td>49</td>
</tr>
<tr>
<td>AIEP</td>
<td>38</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>Phyllodes</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Lobular</td>
<td>12</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>CSL / RS</td>
<td>3</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>Columnar cell</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Mixed</td>
<td>11</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Totals</td>
<td>79</td>
<td>30</td>
<td>239</td>
</tr>
</tbody>
</table>
PPV of B3 CNB  $n = 372/4035$ (9.2%)  

- Excision histology benign  – 181 64.9%
- malignant  – 98 35.1%

Lesion specific ppv % excision ( ) % = excision / follow up

ADH  44.7  (40.6)
LN   60.9  (58.3)
papillary  22.7  (15.9)
CSL  16.7  (12.3)
phyllodes  12.5  (12.5)

Houssami N et al, BJC 2007 96, 1253-1257
PPV of B3 CNB  $n = 523$  (5%)

- Excision histology benign  – 417  80%
  malignant  – 106  20%

Lesion specific ppv %  excision histology

- $ADH$  32
- $LN$  30
- papillary no atypia  4.0
- papillary with atypia/LN  36
- $CSL$ no atypia  9
- $CSL$ with atypia/LN  24

Conservative management of screen detected radial scar – role of mammotome excision

- n = 22 radial scar without atypia

- 14 VAC
  11/14 – diagnosis confirmed
  3 sx - 1 LCIS, 2 technical

- 8 surgery
  1 DCIS

Rajan S et al J Clin Path 2011:64 65-68
VAC excision of breast lesions of uncertain malignant potential (B3) – an alternative to surgery in selected cases

- N = 42 B3 lesions with no atypia
  - papillary – 24
  - radial scar – 18

2 patients upgraded to CA
2 patients with papillary lesions developed ipsilateral CA at 24 and 41 months

*Tennant SL et al Breast 2008 17(6):546-9*