Breast Cancer Staging

Pathology Issues

- Tumour Size
- Vascular Invasion
- Lymph Node Status

Circulation 2001/1 Case 8
Invasive Ca, grade 1, NST

Circulation 2001/1 Case 11
Invasive Ca, grade 2, Lobular
Circulation 2001/1 Case 7 Low grade DCIS

Case No. 7

Distribution of measures of agreement for NHSBSP pathologists

Object A

Object D

No. of pathologists

Maximum diameter (mm)

No. of pathologists

Maximum diameter (mm)
Breast Cancer
Minimum Data Set

Size measurement hierarchy
- Pathological Size
  - Microscopic - impalpable & diffuse tumours
  - Macroscopic verified by microscopy
- MRI
- Ultrasound
- Mammography
- Clinical

VI in Breast Cancer

Prognostic significance
- Close correlation with loco regional lymph node status
- Correlation with early recurrence in lymph node negative patients
  Rosen et al, 1982; Bettelheim et al, 1984
- Predicts for long term survival, independent of nodal status
  Rosen et al, 1982; Pinder et al, 1994
- Predicts for local recurrence following breast conservation therapy
  Nealon et al, 1981; Rosen, 1983; Locker et al, 1989
- Predicts for flap recurrence after mastectomy
  O'Rourke et al, 1994

Vascular Invasion in Breast Cancer

Frequency

<table>
<thead>
<tr>
<th>Study</th>
<th>% cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al, 1975</td>
<td>33</td>
</tr>
<tr>
<td>Roses et al, 1982</td>
<td>21</td>
</tr>
<tr>
<td>Davis et al, 1985</td>
<td>59</td>
</tr>
<tr>
<td>Dawson et al, 1986</td>
<td>57</td>
</tr>
<tr>
<td>(a) 25 yr survivors</td>
<td>67</td>
</tr>
<tr>
<td>(b) short term survivors</td>
<td>24</td>
</tr>
<tr>
<td>Orbo et al, 1990</td>
<td></td>
</tr>
<tr>
<td>Pinder et al, 1994</td>
<td>23</td>
</tr>
</tbody>
</table>

Diagnostic Criteria
- Tumour emboli must be present within clear spaces which are lined by endothelial cells
- No distinction is made between lymphatics, capillaries and post-capillary venules
- Assessment is made in breast tissue adjacent to the main primary tumour and not within it
- Topographic patterns are helpful in identifying involved vessels
LVI for LN neg

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

Group 0, Group 1

Time

p = .00017

LVI contribution and nodal status contribution to hazard

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

LVInegLNneg, LVIposLNneg

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

LVInegLNneg, LVIpos 1 and 2

Merging LVI pos 1 and 2

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

LVInegLNneg, LVIpos 1 and 2

Merging LVI pos 1 and 2

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

LVInegLNneg, LVIpos 1 and 2

Merging LVI pos 1 and 2

Cumulative Proportion Surviving (Kaplan-Meier)

Complete   Censored

LVInegLNneg, LVIpos 1 and 2
Lymph node Staging

Background and rationale including the results from clinical trials

Optimal handing of the specimen and analysis

Role of Immunohistochemical analysis?
Role of Intraoperative Examination?

Alternatives and future directions

Lymph Node Involvement in Breast Cancer

- Palpable loco-regional lymph nodes form an important part of TNM clinical staging - notoriously inaccurate - Barr & Baum, 1992
- Presence of histologically confirmed axillary metastases indicates a poor prognosis e.g. 10 year survival reduced from 75% to 30% - Cutler et al, 1969
- The greater the number of nodes involved, the poorer the prognosis - Fisher et al, 1984; Galea et al, 1992

Nottingham Tenovus Primary Breast Cancer Study

Lymph Node Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

Chi-Square 621.486
DF 2
P-Value <.0001

Stage 1: LN Neg
Stage 2: Up to 3 low axillary LN +, or internal mammary LN + alone
Stage 3: 4 or more axillary LN +, or axillary AND internal mammary +

Axillary Surgery

- Staging
- Loco-regional control
- Survival
**Staging and Prognosis**

- ALND
  - Widely accepted
  - Qualitative
  - Quantitative
- Axillary Node Sample
- SLNB

**Loco-regional Control**

Local disease control is essential

NSAPB - 04

- 10 year axillary recurrence rate
- 1% node negative
- 3% node positive with ALND
- 17% node positive, no dissection
- However no survival difference

**Survival**

- Variations between studies
- No difference - NSABP B-04
- Advantage
  - Cabanes et al - 5 year
  - Guys hospital, Edinburgh - long term
- May have some impact but quality of evidence poor

**Advantages of ALND**

- Most important prognostic variable
- Planning of adjuvant systemic therapy
- DFS and OS are related to number of involved nodes
- Node positivity increases with tumour size
- But screening detects smaller cancers likely to be node negative

**Disadvantages of ALND**

- Seroma
- Wound infection @10%
- Reduced shoulder mobility
- Damage to motor nerves
  - Medial pectoral
  - Long thoracic
  - Thoracodorsal
- Numbness and paraesthesia
- Lymphoedema - 10 - 25% (30 - 40% if ALND + RT)

**Sentinel Lymph Node**

- Definition
  - "Any node receiving direct lymphatic drainage from the primary tumour"
SLNB
- Constant afferent channel to SLN
- Assumes skip metastases do not occur (< 5%)
- Negative SLN implies negative entire lymphatic basin
- Minimally invasive
- Less morbidity
  - ALMANAC trial

Operative Appearance
- a blue node
- a hot node
- a palpable node

What to do if SLNB +ve?
- In 50 - 70% the SLN is the only involved node
  - Staged and treated by SLNB
- 30 - 50% have micro or macro-mets in non sentinel nodes
- ALND or RT?
- Consider volume of nodal disease, patients factors, patient wishes
- Discuss pros and cons of each procedure fully
- No right or wrong answer!

Natural History of Nodal Mets
- May progress and lead to relapse and decreased survival
- May be adequately treated by adjuvant systemic therapy
- May be ablated by radiotherapy
- ACOSOG - Z0011 - no survival advantage to ALND if SLNB +ve

Conclusions
- SLNB has largely replaced ALND for most early breast cancer patients
- ALND will increasingly be limited to patients with more extensive axillary disease and to those with local recurrence
- Further study is needed to evaluate the clinical significance of IHC-detected isolated tumour cells and micro-metastases in sentinel nodes.

Sentinel lymph node biopsy
Background and rationale including the results from clinical trials
Optimal handing of the specimen and analysis
  - Role of Immunohistochemical analysis?
  - Role of Intraoperative Examination?
Alternatives and future directions
**Conclusion from surgical / pathological validation studies**

- The sentinel lymph nodes (SNs) are the most likely sites of regional nodal metastases.
- This status provides us (pathologists) with the possibility of concentrating our efforts on them.

**Stand alone SLNB has resulted in intense scrutiny of the 1-2 nodes presented to pathology.**

- There is a need for uniformity of reporting and data collection.
- Recent survey in Europe revealed 123 different protocols for SLNB.
  - When is a negative SLN negative?
    - Levels H and E (63%)
    - IHC (71%) 12 different antibodies
    - Molecular analysis (4%)

**Lymph nodes and micrometastases**

- Axillary lymph node status
  - Assessed by single H and E section is an independent prognostic variable.
- Further pathological examination
  - Multiple levels H and E
  - And/or Immunohistochemistry reveals "micrometastatic" disease in 10-30% of LN

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Improved staging due to „enhanced” histopathology
Methods of increasing detection of nodal metastases

- Identifying more nodes in specimen
- Cutting node into smaller pieces
- Step sections or levels
- Immunohistochemistry
- Reverse transcriptase polymerase chain reaction (RT-PCR)

Trends and possibilities in SN assessment

SLN assessment

Standard histopathology
Enhanced histopathology

Limited sampling with or without IHC
Thorough (systematic) sampling

“Standard” assessment

“Standard” histopathology
- Many of the earliest reports, and some clinical trials use this approach.
- “Standard” is often 1 level / SN, but can be multiple levels / SN depending on the institution. Rarely is it specified.

“Standard” histology of LNs

At some places standard assessment is multilevel, at others it is 1 HE.


Trends and possibilities in SN assessment

SLN assessment

Standard histopathology
Enhanced histopathology

Limited sampling with or without IHC
Thorough (systematic) sampling
“Enhanced” histopathology

- Multilevel assessment:
  - Serial sectioning (at least 3 meanings) - preferred terminology:
    - Slicing (gross)
    - Step sectioning
    - Serial sectioning (microscopic)
  - Immunohistochemistry (CKs):
    - Generally containing CK8/18 (e.g. AE1/AE3, MNF116, CAM5.2...etc)
  - Combination of these two

Multilevel assessment I.

- A few mm thick slices
- 2-3 mm apart
- This means the assessment of an HE section per each level from a few tissue blocks (often embedded in one cassette).
- Terms: - Slicing, macroslicing, macroscopic slicing

Multilevel assessment II.

- This means the assessment of microscopic levels at specified distances from each other (complete or incomplete assessment of the blocks).
- Terms: - Step sectioning

Multilevel assessment III.

- This means the assessment of microscopic levels separated by the thickness of one (or a few) sections (complete or incomplete assessment of the blocks).
- Terms: - Serial sectioning, microscopic serial sectioning

Multilevel assessment IV.

- A combination of slicing and step sectioning
- 4 slices of an obviously positive SN, not requiring step sectioning
- 3 slices step sectioned at 250 mm
**Immunohistochemistry**

- Increases detection of metastases by 10 to 30%
- Quicker for technician and pathologist
- Can assess morphology
- Pitfalls

**sentinel node trial**

- **ACOSOG Z0010**
- 5539 patients
- BCT and SNB (AxCl if LN+(H&E))
- 5 year OS not related to nodal mets discovered with immuno (trend for BM mets) on multivariate analysis

**Trends and possibilities in SN assessment**

**Limited sampling with or without IHC**

- A few levels separated by a given distance.
- Results in upstaging but leaves a proportion of the SN unexplored
- E.g. the Santa Monica protocol

**The Santa Monica protocol (2004)**

Halving of the lymph node in its hilar plane, which they claim to be the most likely site of metastases.

- 1 HE frozen
- 1 HE paraffin
- 1 CK IHC separated by 200 mm from the initially assessed level (per half)
- Efferent lymphatics
- Rather large proportion of the SN not investigated
**Trends and possibilities in SN assessment**

- **SLN assessment**
  - Standard histopathology
  - Enhanced histopathology
  - Limited sampling with or without IHC
  - Thorough (systematic) sampling

**Thorough (complete)sampling**

- The whole thickness of the SN is investigated at given distances, depending on the size of the metastases we are looking for.
- Complete (?) investigation of the lymph node. (Loss of diagnostic material)

\[ z_a = 2\left(\frac{r^2}{d^2}\right)^{1/2} \]

**Complete step sectioning of SNs at 250 mm + IHC /750 mm**

- To detect a spherical metastasis of 2 mm in diameter as a metastasis of 2 mm, levels separated by 1 mm should be examined.

\[ z_a = 2\left(\frac{r^2}{d^2}\right)^{1/2} \]

- \( d \): distance between sectioning levels

**Statements on handling**

- Thorough (systematic) sampling may yield the best results.
- The largest metastases are generally detected by limited sampling.
- IHC may sometimes be of help in identifying larger metastases, but it generally helps detecting micrometastases and ITCs.

**Pathology assessment of SLN: National guidelines**

- All SLN assessed separately
- Management of
  - Nodes <4mm
  - Nodes >4mm
- Standardised reporting
**Pathology assessment of SLN: National guidelines**

- Single H & E section
  - Suspicious or metastatic cells seen?
  - Further levels and/or ICC to establish nature and size (classification) of deposit
  - IHC may be helpful but not mandatory
  - Identification of ITC not the aim of assessment

**Micrometastasis**

- Term introduced by Andrew Huvos; <2mm, as this was felt the size that generally needed microscopy for detection. Larger metastases could more often be picked up by experienced naked eye examination.
- However the term is used differently by different authors.

**The current definitions of ITC (and micrometastasis)**
TNM categories are arbitrarily chosen (have some evidence in support), but are used on the basis of a consensus. They have DEFINITIONS, but these are not sufficient to assure an acceptable reproducibility.

Micrometastasis (UICC) 
pN1mi

- Larger than 0.2 mm, but none larger than 2 mm in greatest dimension


Studies of occult metastases with at least 40 events or 150 patients

Micrometastasis (UICC) 
pN1mi

- Larger than 0.2 mm, but none larger than 2 mm in greatest dimension


pNO & isolated tumor cell clusters (ITC)

- Approximately 1,000 tumor cells are contained in a three-dimensional 0.2 mm cluster. Thus, if more than 200 individual tumor cells are identified as single dispersed tumor cells or as a nearly confluent elliptical or spherical focus in a single histologic section of a lymph node there is a high probability that more than 1,000 cells are present in the lymph node. In these situations, the node should be classified as containing a micrometastasis (pN1mi).

- The 200 cells must be in a single node profile even if the node has been thinly sectioned into multiple slices.

- It is recognized that there is substantial overlap between the upper limit of the ITC and the lower limit of the micrometastasis categories due to inherent limitations in pathologic nodal evaluation and detection of minimal tumor burden in lymph nodes. Thus, the threshold of 200 cells in a single cross-section is a guideline to help pathologists distinguish between these two categories. The pathologist should use judgment regarding whether it is likely that the cluster of cells represents a true micrometastasis or is simply a small group of isolated tumor cells.

- Metastatic characteristics no longer considered in the distinction between micrometastasis and ITC.

Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. Weaver. Mod Pathol 2010

“All protocols that use serial sections and IHC must be considered experimental until validated with outcome data”

Sectioning nodes at 2mm intervals
Embedding all the sections
Examine one section


3887 women (NSABP-B32), median follow up 95 months
Sentinel node (+/- Axillary Clearance)
2mm slices, H&E negative
Immuno at 0.5mm and 1mm, but clinicians not informed
Occult metastases 16%
5 year overall survival:
Occult metastases present 94.6%
Occult metastases not seen 95.8%
Multivariate analysis (with size and grade, but no VI):
Occult metastases RR 1.4 (95% 1.05 – 1.86)
Conclusion: ‘do not indicate a clinical benefit of additional evaluation, including immunohistochemical analysis’
Intraoperative Assessment
- Frozen section
- Imprint cytology
- Intraoperative immunohistochemistry
- Molecular assessment

Sentinel lymph node biopsy
Background and rationale including the results from clinical trials
Optimal handing of the specimen and analysis
Role of Immunohistochemical analysis?
Role of Intraoperative Examination?
Alternatives and future directions

Imaging modalities for assessing the axilla
- Mammography
- CT
- MRI
- PET
- Scintimammography
- Ultrasound
Pre-operative Biopsy of Axillary Lymph Nodes

Cortex

Benign  Malignant

- Normal  94% 10%
- Abnormal 6% 90%

P<0.0001

In vitro high Resolution Helical CT of small axillary Lymph Nodes in Patients with Breast Cancer. Uematsu et al AJR 2003;176:1069-1074

Pre-operative biopsy of axillary nodes

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of pts</th>
<th>No. with LN mets (%)</th>
<th>FNA/ Core</th>
<th>Criteria used</th>
<th>pre-op diagnosis rate (%)</th>
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<tbody>
<tr>
<td>Bonnema et al (1997)</td>
<td>150</td>
<td>62 (41)</td>
<td>FNA</td>
<td>No</td>
<td>63</td>
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<tr>
<td>de Kanter et al (1997)</td>
<td>185</td>
<td>87 (47)</td>
<td>FNA</td>
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<tr>
<td>Kuenen-Boomeester (2002)</td>
<td>183</td>
<td>85 (46)</td>
<td>FNA</td>
<td>No</td>
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<tr>
<td>Duret et al (2003)</td>
<td>268</td>
<td>121 (45)</td>
<td>FNA</td>
<td>Yes</td>
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<tr>
<td>Damera et al (2003)</td>
<td>166</td>
<td>64 (39)</td>
<td>Core</td>
<td>Yes</td>
<td>42</td>
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<tr>
<td>Ciatto et al (2004)</td>
<td>491</td>
<td>298 (61)</td>
<td>FNA</td>
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<td>73</td>
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Node positive patients

<table>
<thead>
<tr>
<th>No. of positive nodes</th>
<th>No. of patients</th>
<th>% diagnosed by pre-op biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>60</td>
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<tr>
<td>3 or more</td>
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<td>77</td>
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<tr>
<td>4 or more</td>
<td>20</td>
<td>90</td>
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Nottingham data

STUDY CONCLUSIONS

- A pre-operative diagnosis of nodal metastases can be made in 42% of node positive patients
- US guided core biopsy is more sensitive in patients with extensive nodal involvement

Nottingham data

<table>
<thead>
<tr>
<th>Slicing</th>
<th>Step sectioning</th>
<th>IHC</th>
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<tbody>
<tr>
<td>US/CAP</td>
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<td>US/Philadelphia</td>
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<td>UK</td>
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<td>No</td>
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<tr>
<td>Germany</td>
<td>Yes</td>
<td>Yes (500 μm)</td>
</tr>
<tr>
<td>Austria</td>
<td>Yes</td>
<td>Yes (200 μm)</td>
</tr>
<tr>
<td>Australia</td>
<td>Yes</td>
<td>Yes (4 at 200 μm)</td>
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<tr>
<td>EU Guidelines</td>
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