The Evolution of Sentinel Node Biopsy

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Breast Cancer Treatment

- The future of oncology is to provide maximum disease control with minimum morbidity
Major Points

• Sentinel node mapping works
• Enhanced pathology improves staging accuracy
• Technical factors / surgeon can affect accuracy
• Small deposits of disease probably have some prognostic value
• Node positivity rates are going up and this can be used as a quality indicator
Lymphatic System

“The lymphatic system is often de-emphasized by anatomists on the grounds that it is difficult to see on a cadaver.”
Figure 1-31. Preoperative subareolar injection of Direct Sky Blue. The skin over the central portion of the breast is stained blue.
Figure 1–32. A prepectoral lymph node high up on the upper outer surface of the breast revealed by preoperative subareolar injection of Direct Sky Blue.
Removal and examination of level I/II axillary lymph nodes should be the standard practice in most cases of early breast cancer. This should ideally result in the identification of at least 10 nodes.
Improved Axillary Staging of Breast Cancer with Sentinel Lymphadenectomy

Armando E. Giuliano, M.D., Paul S. Dale, M.D., Roderick R. Turner, M.D., Donald L. Morton, M.D., Sheila W. Evans, R.N., M.S., and David L. Krasne, M.D.

Prospective Groups similar
ALND: routine H&E
SLND: multiple sections + IHC

% node positive

% with micromets <2mm

ALND group (n=134) SLND group (n=162)
When 1087 NSLNs from SLN negative patients were examined, only 1 (0.09%) node was positive.
Enhanced Pathology of SLNs: Serial Sections and Immunohistochemistry

- Increased detection of metastases
- More accurate SLNBs (fewer false negatives)
- Better Treatment
Exclusion of pN0(i+) ("ITC" nodes) or pN1(mic) lowers the SLN positivity rate.

Enhanced pathology (IHC) improves accuracy by lowering FN rate.
Breast Cancer SLN Validation Series

False Negative Rate (%)

Size of SLN Met Counted as Positive

- Any Size
- Exclude < 0.2 mm
- Exclude < 2.0 mm

- 2.1
- 4.9
- 16
Should SLN Biopsy Be Adopted or Tested?

**Adopt SLNB**
- If axillary dissection is considered only a diagnostic / staging test, then one should just do the SLNB.
- The more important question is whether to use enhanced pathology / IHC.
- Join ACOSOG Z-010

**Test SLNB**
- If one believes that ALND may provide some therapeutic or survival value, then we should evaluate SLNB in a RCT.
- Join NSABP B-32 and also test whether enhanced pathology improves outcome.
Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial

Lancet Oncology 8:881, 2007
- SLNB successful in 97.2%
- Almost all (98.6%) SLN’s were in axilla
- 65% hot and blue, 25% hot only, 5% blue only 5% palpation only
- No IHC
- Accuracy 97.1%
- FN rate 9.8% (CI = 7.8 - 12.2)

Lancet Oncology 8:881, 2007
NSABP B-32

- 2619 pts SLN + ALND
- 29.2 % node positive
- FN rate 9.8%, Accuracy = 97.1%, Sens 91.2%,
RCTs for Node Negative Patients
SLNB vs ALND (+ SLNB)
Surgeon Training

- ALMANAC
  - Validation and randomized phases
- NSABP B-32
  - Training cases prior to surgeon entry
- Sentinella-GIVOM
  - Limited or no training
- Milan
  - Single Institution
False Negative Rates in SLN RCTs

![Bar chart showing false negative rates for different studies (ALMANAC, NSABP B-32, Sentinella, Milan).]
Sentinel Lymphadenectomy Deconstructed

- Patient selection
- Mapping techniques
- Operative options
- Pathologic evaluation
- Management of the ‘positive’ SLN
- Quality assurance
Patient Selection For Sentinel Lymphadenectomy

- Isolated DCIS: No
- Positive nodes: No
- DCIS requiring mastectomy: Yes
- Isolated invasive carcinoma: Yes
- Prior lumpectomy: Yes
- Multicentric carcinoma: Yes
- Large (T3) invasive cancers: Yes
- After preoperative chemotherapy: Yes
Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: Guideline Recommendations


A Quality Initiative of Cancer Care Ontario’s Surgical Oncology Program (SOP) and Cancer Care Ontario’s Program in Evidence-Based Care (PEBC)

Report Date: July 14, 2009

“SLNB is recommended as the preferred method of axillary staging for all patients with a clinical presentation of early breast cancer in the absence of clinically or pathologically positive lymph nodes.”
NSABP B-32 Technique:

- intradermal Tc-99m sulfur colloid
- peritumoral Tc-99m sulfur colloid
- peritumoral Lymphazurin
Intradermal Radiocolloid and Intraparenchymal Blue Dye Injection Optimize Sentinel Node Identification in Breast Cancer Patients

NSABP B-32 Technique:
- intradermal Tc-99m sulfur colloid
- peritumoral Tc-99m sulfur colloid
- peritumoral Lymphazurin
- Patent Blue
- Periareolar
Operative Technique

- Drape the arm free
  - Allows easy access to harder nodes
- Small incision just inferior to hair line
- Don’t fry the Sentinel node
  - Watch the cautery
- Line of sight to the hot node
  - Pick up both sides of hot line and cut between, repeat until node is seen
## Criteria For SLN Removal

Multi-institutional Study on Breast Cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>False Negative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only hottest node</td>
<td>13.0 %</td>
</tr>
<tr>
<td>Hottest node and all blue nodes</td>
<td>8.7 %</td>
</tr>
<tr>
<td>All nodes greater than 10% of hottest and all blue nodes</td>
<td>5.8 %</td>
</tr>
</tbody>
</table>
• Review our recent data (97-06) and results
• Attempt to optimize procedure
  ▪ Check the 10% rule
  ▪ Reduce the number of SLN ’s harvested but still maintain accuracy
  ▪ Determine whether we need to chase level II SLN ’s

Sentinel Nodes in Breast Cancer: Relevance of Axillary Level II Nodes and Optimal Number of Nodes that Need to Be Removed

Jean-François Boileau, MD, MSc,¹ Alexandra Easson, MD, MSc,¹ Jaime M. Escallon, MD,¹ Wey L. Leong, MD,¹ Michael Reedijk, MD, PhD,¹ Bruce J. Youngson, MSc, MD,² and David R. McCready, MD, MSc¹

Annals of Surgical Oncology, 2008
893 Sentinel Lymph Node Biopsies

- 97.4% rate of technical success (870 of 893)
- False negative rate: 4.3% (4/94)
- 287 ‘positive’ SLNs in 870 SLNBs (33 %)

Size of Nodal Metastases:
- N0i+ (<0.2mm)
- N1mi (0.2-2mm)
- N1 (>2mm)
All Node Positive Patients Were Accurately Staged In The First 4 SLN’s
One can safely ignore a hot ‘level 2’ node unless
• it is the only node
• the count is similar to the hottest level I node

<table>
<thead>
<tr>
<th>Radioisotope threshold</th>
<th>Undetected positive SLNBs (N)</th>
<th>Percentage of undetected positive SLNB (%)</th>
<th>False negative rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>–</td>
<td>–</td>
<td>3.3</td>
</tr>
<tr>
<td>20%</td>
<td>4</td>
<td>2.1</td>
<td>5.4</td>
</tr>
<tr>
<td>30%</td>
<td>6</td>
<td>3.1</td>
<td>6.4</td>
</tr>
<tr>
<td>40%</td>
<td>8</td>
<td>4.1</td>
<td>7.4</td>
</tr>
<tr>
<td>50%</td>
<td>12</td>
<td>6.2</td>
<td>9.5</td>
</tr>
<tr>
<td>100%</td>
<td>17</td>
<td>8.8</td>
<td>12.1</td>
</tr>
</tbody>
</table>

N = 193 patients.
Technical Findings

- Stick to the 10% Rule
- Stop at 4 nodes
- Ignore hot ‘level 2’ nodes
  - unless it is the only node
  - unless the counts are similar to the hottest level I node
Management of Positive SLN
Rate of NSLN Disease at PMH

- Total patient number: 870
- SLN positive patients: 287
  - <=0.2mm: 62
  - >0.2-2mm: 64
  - >2mm: 161
- SLN true negative: 579
- SLN false negative: 4
- # SLN positive (size largest metastases):
  - # SLN positive: 9 of 64 (14%)
  - # with non SLN positive > 0.2 mm: 68

Completion ALND after finding micrometastases 0.2 - 2mm in SLN’s, revealed **9 of 64 (14%)** patients had significant residual axillary disease.
Completion ALND after ‘isolated tumor cells/clusters’ in SLN’s, revealed 2 of 39 (5.1%) patients had significant residual axillary disease.
Case SNMM

- 0.9 cm IDC NOS, Grade 2/3
- ER ++, PR + , HER 2 neg
- LVI present
- SLN showed several nests of tumor mets < 0.02 cm on H&E in subcapsular sinus, confirmed with IHC

Case 35-2005 NEJM 2005;353:20
Table 3. Memorial Sloan-Kettering Cancer Center Nomogram for Prediction of Additional Axillary-Node Disease in the Patient.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size</td>
<td>0.9 cm</td>
</tr>
<tr>
<td>Type and grade</td>
<td>Ductal; 2</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Yes</td>
</tr>
<tr>
<td>Multifocal</td>
<td>No</td>
</tr>
<tr>
<td>Estrogen-receptor expression</td>
<td>Positive</td>
</tr>
<tr>
<td>No. of positive sentinel nodes</td>
<td>1</td>
</tr>
<tr>
<td>No. of negative sentinel nodes</td>
<td>0</td>
</tr>
<tr>
<td>Method of detection of metastases</td>
<td>Staining with hematoxylin and eosin, serial section</td>
</tr>
</tbody>
</table>

The MSK nomogram predicts a risk of additional (macro) metastases (eg 19%)
Case SNMM: pT1b, pN0 (i+), M0

after Morrow

- Completion ALND?
  - risk of additional positive nodes: 19%
  - risk of regional recurrence: 3 - 10%
  - sequelae of treatment
  - potential impact of local therapy on survival
  - impact on other treatment decisions

AdjuvantOnline! predicts 10-year survival benefit of <1% if N0 and up to 5% if N1 with chemo

Case 35-2005 NEJM 2005;353:20
Occult Axillary Node Metastases in Breast Cancer Are Prognostically Significant: Results in 368 Node-Negative Patients With 20-Year Follow-Up

Lee K. Tan, Dilip Giri, Amanda J. Hummer, Katherine S. Panageas, Edi Brogi, Larry Norton, Clifford Hudis, Patrick I. Borgen, and Hiram S. Cody III

- 368 node negative patients: 1976-78
- Mastectomy + ALND, no systemic Rx
- SLN protocol used on ALN blocks at MSK
- 23% (83/368) upstaged
  - 73% : ≤ 0.2 mm       pN0 i+
  - 20% : 0.3 - 2.0 mm    pN1 mi
  - 6%   : >2.0 mm        pN1 a
DFS by Largest Cluster Size

No. at risk (# events)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>241 (35)</td>
<td>199 (48)</td>
<td>140 (51)</td>
<td>32 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.2 mm</td>
<td>46 (14)</td>
<td>34 (19)</td>
<td>28 (21)</td>
<td>8 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3–2.0 mm</td>
<td>10 (7)</td>
<td>7 (10)</td>
<td>4 (10)</td>
<td>0 (10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Has the Use of SLNB Changed the Node Positivity Rate for Early Breast Cancers?

Three Scenarios for Nodal Positivity Rate:

- Rate decreases due to increased FN results
- Rate increases due to enhanced pathology, detection of unusually located nodes
- No change: enhanced pathology balanced by FN rate
Axillary Staging for T1 Breast Cancers: SEER 1998 - 2003

N=50,000
Prevalence of Node Positivity in T1 Breast Cancers

- SNB introduced

P<0.0001
Prevalence of Node Positivity [N1(mic) and N1] in T1 Breast Cancers

SNB introduced

% Node Positive

Year


T1a  
T1b  
T1c  

SNB introduced
The increased node positive disease was detected by SLNB.
Summary

- SLNB accurate and recommended
- IHC and multiple sections improve detection, primarily of deposits < 2 mm
- Technical factors important
- LN micrometastases probably have prognostic value
- N1 stage increasing