Problems and Pitfalls of Sentinel Node Biopsy

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Sentinel Node Biopsy - Breast Cancer

- SLNB is associated with a lesser morbidity than standard axillary node dissection in terms of lymphedema and sensory deficits
- Nodal status is the most powerful predictor of long term survival and essential information for determining adjuvant therapies
- SLNB is an accurate staging of nodal status

Sentinel Lymph node Biopsy

- Axillary node dissection is the “gold” standard for axillary staging
- ALND has a false negative rate of up to 5%
- False negative rate of SLNB should be less than 5% to be considered accurate
- Routine level 1 and 2 node dissection can be eliminated for negative sentinel nodes

Indications for SLNB

- Clinically node negative
- Contraindications:
  - pregnant or breast feeding
  - severe allergies
  - DCIS
  - ? T3 tumors
  - ? Previous surgery-augmentation or reduction

Technique

- Injection of radionucleotide (Te sulphur colloid)
- Scan at nuclear medicine dept
- Injection of blue dye –Lymphozurin (isosulfan blue) in operating room
- Scan with probe
- Remove blue and hot nodes

Nuclear Medicine Scan
**Sentinel Node Biopsy**

**Problems**
- Training
- Institutional-nuclear medicine dept - pathology dept
- Logistical – timing, probe access, etc
- Intraoperative pathology
- Team approach

**Institutional**
- Need access to nuclear medicine
- Pathology department needs to be aware of the technique of processing the nodes

**Logistical**
- Timing of injection
day of surgery?
day before surgery?
intraoperative? Need to be able to work with radioactive isotopes
- Timing when associated with fine wire localization

**Training**
- Learning of technique
  - residency
  - post residency
- Difficult to get time to mentor
- Should competency be 20 cases or 5 cases with ALND?
- Guidelines in place
Logistical

- Type of injection
  - peritumoral
  - subdermal
  - subareolar
- Radionucleotide only
- Blue dye
- Both

Type of Injection

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Technique</th>
<th>Identification rate (%)</th>
<th>False-negative rate (%)</th>
<th>Contraception rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>King</td>
<td>443</td>
<td>Tc</td>
<td>91</td>
<td>11</td>
</tr>
<tr>
<td>Bergey</td>
<td>130</td>
<td>Tc</td>
<td>94</td>
<td>7</td>
</tr>
<tr>
<td>Guarino</td>
<td>147</td>
<td>Dye</td>
<td>72</td>
<td>6</td>
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<tr>
<td>Giordano</td>
<td>174</td>
<td>Dye + Tc</td>
<td>65.5</td>
<td>11</td>
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<tr>
<td>McManus</td>
<td>490</td>
<td>Tc + Dye</td>
<td>90</td>
<td>8.3</td>
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<td>Guerech</td>
<td>145</td>
<td>Tc</td>
<td>71</td>
<td>9.7</td>
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<tr>
<td>King</td>
<td>147</td>
<td>Tc</td>
<td>75.8</td>
<td>6.9</td>
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<td>Titus</td>
<td>525</td>
<td>Tc + Dye</td>
<td>87</td>
<td>13</td>
</tr>
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<td>Franks</td>
<td>132</td>
<td>Tc</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>Negash</td>
<td>679</td>
<td>Tc + Dye</td>
<td>94</td>
<td>16.2</td>
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<tr>
<td>Buss</td>
<td>180</td>
<td>Tc + Dye</td>
<td>93</td>
<td>1.9</td>
</tr>
<tr>
<td>Koblar</td>
<td>113</td>
<td>Tc + Dye</td>
<td>83</td>
<td>6.5</td>
</tr>
</tbody>
</table>
| Dye, Blue dye, Tc, radionucleotide injection.

Type of Injection

Table 1. Subareolar Injection: Validation Studies with Microsz 3100 Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>First author</th>
<th>n</th>
<th>Identification rate (%)</th>
<th>False-negative rate (%)</th>
<th>Contraception rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation</td>
<td>McManus</td>
<td>85</td>
<td>99</td>
<td>53</td>
<td>--</td>
</tr>
<tr>
<td>Krueger</td>
<td>60</td>
<td>98</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Joffres</td>
<td>15</td>
<td>100</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Reban</td>
<td>245</td>
<td>96</td>
<td>--</td>
<td>90</td>
<td>--</td>
</tr>
<tr>
<td>Kleinberg</td>
<td>64</td>
<td>94</td>
<td>--</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>Titus</td>
<td>159</td>
<td>100</td>
<td>--</td>
<td>90</td>
<td>--</td>
</tr>
<tr>
<td>King</td>
<td>130</td>
<td>96</td>
<td>--</td>
<td>95</td>
<td>--</td>
</tr>
</tbody>
</table>

Specific problems

Related to the surgical procedure

Blue Dye (Lymphozurin)

- Tattoo effect
- Blue breast (may last for months)
- O 2 sat’s down in OR
- 80% accuracy if used alone
- Allergic reactions
Blue Dye

Blue Breast

Blue Dye - Methylene Blue

- Less expensive
- Can be associated with skin necrosis

Allergic Reactions

- Case 1
  Ms. J., 28 female with .8 cm tumor in upper outer right breast. Taken to OR and injected with 5ml lymphozurin. Axillary incision made. Anesthesiologist outside door talking and rushes back to room as BP drops to 50. Patient has slight rash. No other changes. Given steroids, benedryl, etc and BP comes up. Surgery completed. ICU overnight with no adverse outcome.

- Case 2
  Mrs. G, 78 yr old with 1.5 cm tumor left breast. Has had previous MI 5 years prior. Otherwise in good health. OR procedure to be partial mastectomy and SLNB. Becomes hypotensive during case about 10 minutes after injection of lymphozurin. Difficult for anesthesiologist to determine cause and difficult to get pressure back up. Eventually case finished. Patient to ICU and had multiple problems with multiple organ failure. Eventually recovers after 10 days in ICU. Out of hospital in one month.

### Allergic Reactions

Table 1. Selected Studies of Allergic Reactions to Blue Dye

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Blue dye type</th>
<th>% of cases (type)</th>
<th>Incidence (%)</th>
<th>No. of severe reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopes et al., 2000</td>
<td>Iodine blue</td>
<td>1 (methylene blue)</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Cannata et al., 2001</td>
<td>Iodine blue</td>
<td>1 (methylene blue)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Alman, 1994</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.1</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Montgomery et al., 2002</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>Bhowmik et al., 2002</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>Leary et al., 2002</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>Rodin and Associates, 2002</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
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<tr>
<td>Cordes et al., 2001</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
</tr>
<tr>
<td>Spring et al., 2001</td>
<td>Iodine blue</td>
<td>11 (methylene blue)</td>
<td>1.0</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: Includes cases of lymphatic mapping performed for breast cancer.

Any text that is not part of the content is not relevant and should be ignored.
Blue Dye Summary
- There is a move away from using blue dye in experienced hands
- Still useful in ease of identification (especially in obesity)
- Useful for teaching
- Can pre-medicate with steroids and benedryl

Failure to image nodal drainage on scan
- Not usually a problem
- Positive nodes tend to be found at the time of operation
- Blue dye may be effective in localization
- If nothing at all found should do ALND

Unusual sentinel location

Technique failure
- Ms. L 54 yr old with susp calcifications on right mammogram. FNA done HK shows malignant cells.
- FWLB done showing DCIS multifocal, extensive and ER +ve so goes on to mastectomy with SLNB and immed recon. Hot and blue fat identified. No abnormal nodes so ALND not done (DCIS only)
- Final path 2.5mm HER 2 +ve invasive cancer and DCIS. All margins clear. Do you go back for ALND?

Failure of technique
- Nothing on scan from nuclear medicine
- Nothing to find with probe
- No blue dye uptake
- Happens about 3-5% of the time
- Do ALND

Scan with multiple nodal sites
Scan with multiple nodal sites
- Surgery should involve sentinel node biopsy of axillary nodes - go up to level 3 if needed
- Document rest of drainage pattern

Internal Mammary Lymph Node Biopsy
- Bleeding
- Pleural effusion
- Pneumothorax
- Costochondritis
- Unisightly scar

Internal Mammary Node Biopsy – Halsted Revisited
- IM nodes found to be positive in approx 23% of patients
- Almost all concomitant with axillary node metastases
- Metastases alone in IM chain occur in 2-11%
- Extended radical mastectomy abandoned in the 1970’s because of low rate of IM metastases in the absence of axillary mets and removal of all the IM nodes (with no adjuvant treatment) did not improve prognosis

Internal Mammary drainage Position of Tumor

<table>
<thead>
<tr>
<th></th>
<th>Upper outer</th>
<th>Inner/central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uren</td>
<td>28%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Johnson</td>
<td>12.5%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Byrd</td>
<td>15%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Internal Mammary Nodes Change of Treatment
- 7 studies of biopsy of IM SLN performed found SLN metastases in 18% (15/83) who underwent biopsy
- Of these 15 only 2 were negative in the axillary nodes
- There was a change in treatment in 2.4% of patients
- If 1/3 were to get added benefit from adjuvant treatment there would be potential benefit in 0.8% of these patients

Only positive node drainage is Internal Mammary
- No clear guidance
- If an IM node is positive, the vast majority of women will also have axillary node metastases. Therefore, it is advisable to do an ALND
Multiple Nodes

- When to stop?
- What is the ideal number of nodes to obtain?
  - One is probably not enough in most cases.
  - Three seem ideal.
  - Ten is too many.

Optimal number of nodes

<table>
<thead>
<tr>
<th>Low (2006)</th>
<th>113 pts</th>
<th>33% positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st node</td>
<td>87.9%</td>
<td>Accuracy</td>
</tr>
<tr>
<td>2nd node</td>
<td>97%</td>
<td>Accuracy</td>
</tr>
</tbody>
</table>

Wong (2001)

<table>
<thead>
<tr>
<th>1436 pts</th>
<th>Sloan Kettering</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st node</td>
<td>14%</td>
</tr>
<tr>
<td>2nd node</td>
<td>False negative  4.3%</td>
</tr>
</tbody>
</table>

Optimal number or nodes

Factors Influencing Successful SLN Identification

- Should be able to obtain 95% identification rate.
- There is failure of the technique in the best of hands.
- Plan to do ALND if mapping fails.
- Biopsy technique, tumor size, tumor location, cell type and surgeon experience not predictors of mapping failure.

Technical problems

- Obesity - difficult to find nodes.
  - Mapping failure.
- Get into bleeding.
- Hot fat (not nodes).
- Blue everywhere.
- Radioactivity everywhere.
- Multiple nodes positive (when to stop?)
- No nodes identified (do ALND).
Predictors of technique failure
- Obesity
- Elderly
- Multiple nodes “full” of tumor so lymphatics “plugged” and do not allow passage of dye or radionuclide
- Previous wide surgery of upper outer quadrant of breast

Advice for Accurate Staging
- Remove all nodes that are “hot”
- Remove all nodes that are blue
- Put in finger and remove all nodes that feel suspicious

Example of positive finger test
- Ms. C. 50 yr old Asian physiotherapist with 1 cm tumor detected by mammography. Core Biopsy grade 2 invasive cancer. Surgery booked as fine wire guided partial mastectomy and SLN biopsy. At surgery one hot and blue node easily identified. Finger in rest of axilla felt very abnormal. 10 hard nodes removed and ALND completed. The only node negative for metastases was the sentinel node.

Sentinel Node Biopsy in DCIS
- Generally not recommended
- However, if DCIS extensive and mastectomy done is a reasonable option as cannot do later if a small amount of invasion is found on the final pathology. Especially recommended if mastectomy is followed by immediate reconstruction.

Why do Sentinel Node Biopsy
- Less morbidity
- Avoid harvesting negative nodes
- Better staging-nodes can be in unusual places as level 3 or intra-mammary

Example of better staging
- Mrs. A 65 yr old with 2.5cm invasive ca right upper breast. Severe bronchiectasis and allergies. After discussion with radiation oncology decided to have partial mastectomy and ALND. Pathology showed 14 nodes negative but margins close. Decided for completion mastectomy. Had node in tail of breast positive for malignancy. Probably would have identified with SLN biopsy
Ms M (Japanese woman) presented at age 52 with very small, screen detected but difficult to find grade 1, less than 1cm tumor in outer upper quadrant left breast.

SLN biopsy done as well as partial mastectomy. Three sentinel nodes harvested—one level 1 and two at different areas of level 2 axilla. All nodes positive for metastatic cancer. Tumor in breast 1 cm low grade widely excised.

Who?
When?
Will intra-operative pathology help?
What to do about micrometastases?
Predictive modelling

Scarring—much more difficult sometimes
Injury to nerves—sacrifice intercostobrachial nerve
Potential injury to vessels and motor nerves because of dense scar tissue

Most early stage, clinically node negative women are suitable for the procedure
Predict problems pre-operatively
Predict high chance of node positivity and do ALND