SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER

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INTRODUCTION

- Solid tumors - Spread to lymph nodes
- Lymphadenectomy - Part of many curative Cancer operations
- Lymphadenectomy – Staging, Prognostication & Therapeutic
- Changing Concepts – Lymphadenectomy

BREAST CANCER – ALND was the standard technique with excellent therapeutic efficacy and was gold standard in managing the axilla.
CHANGING TRENDS IN BREAST CANCER

CHANGING PATIENT PROFILE

- Breast Cancer - Western world - 70 % Screen detected Non Palpable lesions. In India increasing trend
- Majority - DCIS / T1 and 70 % Node Negative
- Majority receive Adj. Systemic therapy Irrespective of Axillary status

CHANGES IN TECHNOLOGY

- Improvement in quality and accuracy of imaging modalities
CHANGING TRENDS IN BREAST CANCER

CHANGING TREATMENT PHILOSOPHY

- Better Understanding of Breast Cancer Biology
- Paradigm shift - Surgical Approach
  Radical – Conservative
  Old Times - Big Surgeons - Big Incisions- Big resections - ? Big Results - Big Egos
- Functional outcome & QOL issues are important end points
- Add life to years - Years to life
- Critical re-evaluation of ALND Morbidity
The likelihood of axillary LN involvement increases as the size of the primary tumor increases

<table>
<thead>
<tr>
<th>TUMOR SIZE</th>
<th>% WITH LN INVOLVEMENT (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>0.8 %</td>
</tr>
<tr>
<td>T1a</td>
<td>5 %</td>
</tr>
<tr>
<td>T1b</td>
<td>16 %</td>
</tr>
<tr>
<td>T1c</td>
<td>28 %</td>
</tr>
<tr>
<td>T2</td>
<td>47 %</td>
</tr>
<tr>
<td>T3</td>
<td>68 %</td>
</tr>
<tr>
<td>T4</td>
<td>86 %</td>
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</tbody>
</table>

PROBLEMS WITH ALND

- For T1 & T2 disease- 50-70% DO NOT have nodal involvement.
- 50% of patients undergoing ALND develop some complications.

Lymphedema = 15-25%
Intercostobrachial Numbness = 70-78%
Restricted Shoulder Movement = 15-17%
Parasthesia & Seroma Formation
PROLONGED HOSPITAL STAY.
INCREASED MORBIDITY
DIFFICULT TO JUSTIFY IN ALL CASES.

SOLUTION ??

SENTINEL NODE BIOPSY!!
SENTINEL NODE CONCEPT

- Sentinel node refers to the "node on watch."
- The first node in the regional lymph node basin that drains the primary tumor.
- It may not be the one closest to the tumor
- There might be more than 1 SLN.
- If positive, other upstream nodes maybe positive
- Usually there wont be "skip metastasis"
Evolution - Sentinel Lymph Node Biopsy (SLNB)

- Wong et al - 1991 - Anatomic specificity of LN
- Morton -1992 applied this blue-dye technique to lymphatic mapping and sentinel node biopsy in clinically node -ve patients with melanoma
- 1992 - Guliano et al - Blue dye method -Breast cancer
- 1993- Alex & Krag - Gamma probe detection using radio colloid in Breast cancer
Sentinel Lymph node biopsy is becoming an accurate method of staging axillary lymph nodes.

**ADVANTAGES:**

- Reduces patient morbidity.
- Avoids extensive surgeries in patient without nodal metastasis.
- Detects nodal metastasis in early stage.
TECHNIQUES OF SENTINEL NODE BIOPSY

Dye directed (Blue dye) - 1ml Methylene Blue dye injected peritumorally (total of 4 ml), 10-20 mins prior to surgery

Radiotracer directed - Hot node localisation using Gamma probe.

Combination
Technique of imaging Lymphatic flow & Lymph nodes after intradermal injection of a Radiopharmaceutical, which is absorbed by lymphatics.

This method identifies the sentinel node but cannot determine if it is involved with cancer.
Tc99m Sulfur colloid (Unfiltered particle size: 15-5,000 nm)
Filtered- using 0.22-μm filter. Colloid - 100 nm and 220 nm

Tc99m nanocolloid (5-100 nm)

Tc99m Antimony trisulphide colloid (3-30 nm)

Au-198 Gold Colloid

Tc99m Stannous phytate

Tc99m Tilmanocept - CD206 receptor, is 7 nm in size, accumulates in SLNs and is not dependent on particle size. It binds to mannose receptors expressed by reticulendothelial tissue including macrophages and dendritic cells in lymph nodes, which present it to T-cell lymphocytes in lymph nodes. The advantages of this tracer include rapid clearance from the injection depot and low accumulation in second-echelon nodes. Has advantage over colloids in imaging dense breasts.
GAMMA PROBE

Used intraoperatively, in a sterile bag to identify hot nodes during surgery.

Using the images and skin markings as guides, the probe can be used to select the optimum location for incision.

The surgeon uses the probe to guide dissection to the hot node(s) and places the probe in the surgical bed after node excision to confirm removal of the hot node(s).

In working with the probe, it is important to direct the probe away from activity at the injection site.
**SITE OF INJECTION**
- Intraparenchymal
- Sub dermal
- Intradermal
- Peri Tumoral
- Sub Areolar

**TYPE OF INJECTION**
- **Superficial**- easy to perform.
- **Deep**- improved detection of extra-axillary SLNs and the possibility of using a larger injection volume.
- **Both**- may even improve SLN detection and decrease false-negative findings

The site of injection is gently massaged after the administration.
ASCO GUIDELINE RECOMMENDATIONS FOR SENTINEL LYMPH NODE BIOPSY IN EARLY BREAST CANCER
<table>
<thead>
<tr>
<th>Clinical Circumstance</th>
<th>Use of SNB</th>
<th>Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 or T2 tumors</td>
<td>Acceptable</td>
<td>Good</td>
</tr>
<tr>
<td>T3 or T4 tumors</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Multicentric tumors</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>DCIS with mastectomy</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>DCIS without mastectomy</td>
<td>Not recommended except for large DCIS (&gt; 5 cm) on core biopsy or with suspected or proven microinvasion</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Suspicious, palpable axillary nodes</td>
<td>Not recommended</td>
<td>Good</td>
</tr>
<tr>
<td>Older age</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>Obesity</td>
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<td>Limited</td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>Condition</td>
<td>Recommendation</td>
<td>Level</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Evaluation of internal mammary lymph nodes</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>Prior diagnostic or excisional breast biopsy</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
<tr>
<td>Prior axillary surgery</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Prior nononcologic breast surgery (reduction or augmentation mammoplasty, breast reconstruction, etc.)</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>After preoperative systemic therapy</td>
<td>Not recommended</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Before preoperative systemic therapy</td>
<td>Acceptable</td>
<td>Limited</td>
</tr>
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</table>

Abbreviations: SNB, sentinel lymph node biopsy; DCIS, ductal carcinoma-in-situ; ALND, axillary lymph node dissection.

* Levels of evidence: Good, multiple studies of SNB test performance based on findings on ALND; limited, few studies of SNB test performance based on findings on ALND or multiple studies of mapping success without test performance assessed; and insufficient, no studies of SNB test performance based on findings on ALND and few if any studies of mapping success.
**TECHNIQUE**

- L.S. agent used = Tc 99 nano colloid
- Site = Intra Dermal Injection in Sub-Areolar region irrespective of Tumor quadrant.
- Dose = 250-350 micro curie.
- Time = 1-2 hrs before Sx.
- Imaging = performed at 30-60 min after injection
- Intra operatively, surgeon localises the hot nodes using handheld gamma probe.
- All Nodes picked up by Gamma probe were subjected to Frozen section examination.
HOW WE FIND SENTINEL LYMPH NODES?

- Nodes on direct drainage pathway.
- Node with highest counts.
- Count ratio (target to background) > 10
Validation of study

* Learning curve - Short
* Validation study - Minimum of 30 cases as per EANM & SNM joint guidelines

Despite variability in selection criteria and technique, a sentinel lymph node is consistently identified in approximately 96 percent of patients and predicts the status of the remaining axillary lymph nodes in ≥95 percent of patients in most series.


## INTRAOPERATIVE FROZEN-SECTION DIAGNOSIS

<table>
<thead>
<tr>
<th>Authors</th>
<th>H&amp;E sections</th>
<th>N</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False -ve</th>
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<td>96</td>
<td>96</td>
<td>86</td>
<td>100</td>
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<td>98</td>
<td>91</td>
<td>100</td>
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<td>Koller et al</td>
<td>3 consecutive</td>
<td>107</td>
<td>83</td>
<td>64</td>
<td>100</td>
<td>36</td>
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<tr>
<td>Imot et al</td>
<td>Not described</td>
<td>52</td>
<td>96</td>
<td>89</td>
<td>100</td>
<td>11</td>
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<td>GKNMH</td>
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<td>40</td>
<td>95</td>
<td>82</td>
<td>100</td>
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<tr>
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<td>&gt;3</td>
<td>45</td>
<td>93</td>
<td>85</td>
<td>100</td>
<td>15</td>
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<tr>
<td>Noguchi et al</td>
<td>2 mm interval</td>
<td>26</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Motomura et al</td>
<td>1mm</td>
<td>101</td>
<td>88</td>
<td>52</td>
<td>100</td>
<td>48</td>
</tr>
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</table>
A systematic review of 69 trials of SLNB, including 8059 patients, showed that sentinel lymph nodes could be identified in 95 percent of patients with a false negative rate of 7.3 percent (range 0 to 29 percent). Using a combination of isosulfan blue dye and radioactive colloid resulted in a significantly higher success rate and lower false negative rate in sentinel node mapping compared with using isosulfan blue dye alone.


SLNB

- The false negative rate of SLNB was originally reported as being 5 to 10 percent (sensitivity 90 to 95 percent), but lower rates were attained by experienced surgeons.

- Despite initial concerns that this false negative rate would translate into increased axillary recurrence, subsequent trials found that recurrence rates with SLNB were comparable to those with ALND.


Clinical Trials

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, for example, axillary recurrence after SLNB was 0.4 percent with ALND versus 0.7 percent without ALND [1]. Similar findings were demonstrated in the Veronesi study (0 percent with ALND versus 0.8 percent without ALND) [2]. The low axillary recurrence rates in these trials, even without ALND, were presumably due to the effects of adjuvant therapy (chemotherapy or radiotherapy) that may treat residual axillary disease burden.

In patients who did not receive adjuvant therapy or ALND, the axillary recurrence rate was as high as 20 percent, as reported for the NSABP-04 trial [3].

Clinical Trials

SLNB is less morbid for patients than ALND. Several studies have shown that the risk of arm morbidity, particularly lymphedema, sensory loss, and shoulder abduction deficits, is significantly less for SLNB than ALND. In one trial, the risk of lymphedema after 12 months was reported as 2 percent after SLNB alone as compared with 13 percent after SLNB with ALND.

In addition, SLNB identifies patients without axillary node involvement, thereby obviating the need for more extensive surgery for those patients.


NSABP B-32 Trial

5611 early-stage breast cancer patients with clinically negative nodes and compared SLNB followed by ALND with SLNB followed by ALND only if the sentinel lymph node was positive.

SLNB was successfully performed in 97 percent of patients, and the false negative rate was 9.8 percent.

No significant differences were observed in regional control, OS, or DFS between the groups at a median follow-up period of almost eight years.

Primary outcome results of NSABP B-32, a randomized phase III clinical trial to compare sentinel-node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients. ASCO 2010; Abstract LBA505. J Clin Oncol 2010; 28:18s (suppl; abstr LBA505).  
Sentinel node metastases are subgrouped into -

- Isolated tumor cells - small clusters of tumor cells < 0.2 mm
- Micrometastases- metastatic deposit >0.2 mm but <2.0 mm
- Macrometastases - tumor cell deposit >2.0 mm

based upon the size of the largest contiguous tumor deposit present in the sentinel node, as determined by routine histologic examination of slides stained by hematoxylin and eosin.

Immunohistochemistry staining with cytokeratin -not routinely indicated in the pathologic examination of sentinel lymph nodes, IF +VE Occult Metastasis
MANAGEMENT AFTER SENTINEL LYMPH NODE BIOPSY

- Prognostically, patients with Isolated tumor cell clusters appear to do as well as patients without any pathologic node involvement.
- Patients with pN1mi breast cancer have a slightly worse prognosis compared with those with node-negative breast cancer, but micrometastases do not predict recurrence.
- Occult micrometastases have no significance in terms of surgical management and patient outcomes. The NSABP B-32 trial demonstrated that the presence of occult metastases was associated with a 1.2 percent lower OS rate and a 2.8 percent lower DFS rate; patients with occult metastases did not have a higher incidence of regional or distant recurrences.
One or two + lymph nodes

ALND is not necessary in most women with early-stage breast cancer who have only one or two sentinel lymph node metastases and who will receive whole-breast irradiation as part of breast-conserving therapy. If, however, whole breast irradiation is not planned, then ALND is indicated for such patients.

Two randomized trials, the ACOSOG Z-0011 trial and the International Breast Cancer Study Group 23-01 (IBCSG 23-01) trial, demonstrated that many of these patients with one or two metastatic sentinel nodes can safely avoid a completion axillary node dissection.
Sentinel node metastasis with extranodal extension – Completion ALND is still considered the standard of care for patients with extranodal extension of sentinel node metastasis, regardless of the number.

Three or more sentinel node metastases — For patients with three or more pathologically involved sentinel nodes, we recommend a completion ALND for staging purposes and to maximize local control.
Internal mammary nodes

- Internal mammary nodes are only visualized in 20 percent of patients during SLNB partly explained by limitations of the SLNB technique and can be difficult to remove because of their location. Several trials failed to demonstrate a survival benefit with surgical dissection of internal mammary nodes. Positive internal mammary nodes are most commonly found with medial tumors over 2 cm in size.

- Tumor involvement of internal mammary nodes is associated with a poor prognosis. Eight to 10 percent of patients without axillary disease are found to have regional metastases to the internal mammary nodes.
Intramammary nodes

- Intramammary lymph nodes are present in 1 to 28 percent of women with breast cancer.
- Most series report a high likelihood of additional axillary nodal metastases when the intramammary nodes contain cancer.
Axillary reverse mapping (ARM) is an intraoperative technique developed to delineate the lymphatic drainage in the upper extremity during a sentinel lymph node biopsy or axillary lymph node dissection.

When SLNB is done, Axillary reverse mapping (ARM) performed using 2 - 5cc of isosulfan blue, injected into the inner arm prior to skin incision for the axillary lymph node dissection.

The proportion of patients with metastases in the ARM-nodes was significantly higher in patients with proven axillary metastases than in patients with a positive SLN.

ARM node is feasible to identify using radio isotope technique with an excellent sensitivity. It is involved with metastasis (10% cases) only when there are multiple lymph nodal metastases in the axilla.

ARM: axillary reverse mapping – The need for selection of patients P.D.Gobardhan et al volume 38, Issue 8, August 2012, Pages 657-661
Radioguided Occult Lesion Localisation (ROLL)

- 25% of mammographically identified lesions are non-palpable
- ROLL guides precise localisation and excision of these lesions.
- 1 ml (1 mCi) unfiltered 99mTc-Sulphur colloid injected into the breast lesion under USG guidance (WGL not used)
- Ensures complete excision with -ve margin with better Cosmesis and patient compliance
- Can combine SLNB in same sitting - filtered and unfiltered 99mTc-sulphur colloid used

CONCLUSION

The status of the axillary lymph nodes is one of the most important prognostic factors in patients with Breast cancer.

Sentinel Node Biopsy provides accurate staging of Lymphnodes with less morbidity to patients and has become standard of care in the surgical management of early breast cancer.

It requires a multidisciplinary effort involving Surgical oncologist, Nuclear Medicine Physician & Oncopathologist and standardization of the procedure.
Thank You