REVIEW ARTICLE

Sentinel Lymph Node Biopsy : A New Concept in Breast Cancer Management

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Introduction

A sentinel lymphnode (SLN) is defined as the first lymphnode to receive lymphatic drainage from a tumor. This lymphnode is the presumptive initial site of metastatic disease and histologic characteristics of the SLN reflect the histologic charateristics of rest of the basin. The SLN can be identified by injection of a blue dye or radioactive colloid around the primary tumor. Biopsy of SLN can reveal whether there are lymphatic metastasis, thereby obviating the need for extensive lymphnode dissection in patients with SLN free of tumor. Morton *et. al.* (1) were first to demonstrate the feasibility and accuracy of SLN biopsy for nodal staging in patients with melanoma. Since their description, many reports in literature have confirmed the accuracy of this method in identifying lymphnode metastasis in melanoma (2,3). SLN biopsy has largely replaced the elective lymphnode dissection in clinically node negative patients of melanoma and is now considered the standard of care by many (4).

The concept of SLN biopsy was extended to the patients of breast cancer by Giuliano *et. al.* (5) in 1994. They proposed that SLN biopsy might be a good alternative to axillary lymphnode dissection as a staging procedure and could alter the surgical management of axilla in women with breast cancer.

Management of axilla in women with breast cancer has become a controversial issue. The gold standard for assesment of the axillary lymph node status remains the axillary lymph node dissection (ALND). There are two main objectives of axillary nodal staging : (a) It is the most important prognostic indicator of recurrence and survival in breast cancer patients. The presence of nodal metastasis decreases 5 year survival by almost 40% (6,7). (b) The information regarding the number of lymphnodes also helps to determine the type of adjuvant treatment with more aggressive treatment being offered to patients with large number of positive axillary nodes. In addition, axillary lymph node dissection (ALND) has also beeen shown to provide excellent local disease control, which may translate into improved overall survival (8,9).

Other non–invasive methods have not been shown to be sensitive predictors of axillary nodal status. Physical examination of the axilla has a high false positive and false negative rate. Regardless of clinician's experience, upto 35% of patients with clinically negative axilla will turn out to have metastatic disease in axillary nodes

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whereas up to 25% of clinically palpable nodes do not contain malignant cells on pathologic examination. Other investigations like mammogram, ultrasound, Computerised Tomography (CT) scan and Magnetic Resonance Imaging (MRI) cannot differentiate between benign and malignant lymph nodes. Positron emission tomography has been used with 18 – fluoro – 2 deoxy glucose(FDG) to demonstrate primary breast cancer and regional metastasis, the results however are preliminary and the size of detectable lesions or metastasis is not clear (10).

Complete axillary dissection that removes level 1,2,3 nodes, has the highest staging accuracy but is associated with significant morbidity. Pain, paraesthesia, seroma, infection, limitation of shoulder movements and 10-20% incidence of lymph edema are common problems after total ALND (11,12). As many as 80% of women who undergo axillary dissection may have at least one post-operative complication and the psychological distress is common (13). Axillary sampling and level 1 node dissection are associated with less morbidity but high false negative rate of 10-40% (12). Level 1 and 2 ALND causes only 2-3% false negative rate with an acceptable morbidity. In particular the risk of chronic arm edema is only 3-9%, which is considerably lower than that of complete ALND (12). Based on these considerations, the 1990 National Cancer Institute consensus conference recommended level 1 and 2 ALND for patients with potentially curable breast cancer (14). However, with increasing use of screening mammography in western countries, more and more patients are being detected with small (T-1) tumors. These patients have good prognosis and the axillary nodes are rarely involved. Seventy to eighty percent of such patients with early breast cancer will have no axillary nodal metastasis on ALND (12). The benefits of ALND in such patients is being questioned.

Therefore a need was felt to develop an alternative procedure which could accurately determine the axillary nodal status in order to avoid the ALND and its associated morbidity in patients with no metastasis in axillary nodes.

Giuliano *et. al.* (5) adapted the technique used in melanoma to identify the axillary node status in breast cancer patients.

Techniques of SLN localization

(1) *Isosulphane blue dye injection :* The original technique described by Giuliano involves the injection of 3-5 ml of isosulphane blue dye into breast tissue immediately surrounding a primary breast carcinoma or a biopsy cavity. A transverse incision is made in the axilla after 5 minutes just below the hair bearing area of the axilla. Blunt dissection is performed until a lymphatic tract or blue stained node is identified. The dye filled tract is dissected to the first blue node and the tract is followed proximally to the tail of the breast to ensure that the identified node was the most proximal lymph node and thus, the sentinel node. This node is then excised with a rim of surrounding tissues and submitted for histological examination using hematoxylin and eosin staining.

(2) *Radio labelled colloid injection :* This method was described by Veronesi *et. al* (15). One day before the surgery 5-10 MBq of technetium 99m labelled sulfur colloid particles in 0.2 ml saline were subdermally administered immediately above the

breast lesion, followed by 0.2 ml saline with a 25 gauge needle. Planner scans of involved breast and axilla were done 15 min, 30 min and 3 hr after tracer injection. The skin immediately above the first node (sentinel node) that became radioactive was marked. The next day during surgery a hand held gamma ray detector probe was used to locate the sentinel node which was removed using a small axillary incision. Lymph node was then sent for histopathological examination.

(3) *Combination of radiolabelled colloid and blue dye :* This technique was first used by Albertini *et. al.* (16). Here patients came to operation theatre 2-4 hr. after the injection of radiocolloid in the nuclear medicine suite. In operating room 1% isosulphane blue dye is injected around the circumference of the primary tumor 10-15 min before the incision. A hand held gamma detector probe is used for sentinel node dissection. SLN is detected using both visual guidance of blue stained lymph nodes and radioactivity using a hand held gamma detection probe.

Results

Results are summarized in Table 1. The detection rate of sentinel nodes by using blue dye method in different series has varied from 66-93% (5,7,18,21). Most authors have reported that detection rate increases with experience. Giuliano *et. al* (5) in their series reported a detection rate of 66%. They experienced a definitive learning curve. The SLN detection rate was 58% in first half of cases, which increased to 72% in the second half. All false negative sentinel nodes occurred in the first part of this study, sentinel nodes identified in the second half were 100% predictive. In another study by same author comprising 107 consecutive previously unreported patients with T_1 and T_2 tumors, detection rate was found to be 93%. There were no false positive or false negative sentinel nodes and SLN was 100% predictive of axillary metastasis (13). Using the same technique (blue dye) Dale *et. al* (20) and Flett *et. al.* (21) reported a detection rate of 66% and 82% respectively. In the series reported by Flett *et. al.* there was 5 % false negative rate. The sensitivity and specificity of sentinel node was 83% and 100% respectively. The detection rate of SLN was found higher in different studies that used radiolabelled colloid (13,15,19,22,23). Veronesi *et. al.* (5) who used intradermal injection of technitium labelled albumin showed a detection rate of 98%. He had a false negative rate of 5%, sensitivity and specificity were 95% and 100% respectively. Borgestein *et. al.* (22) using peritumoral technitium labelled albumin successfully identified sentinel node in 94%, with a false negative rate of 1.7%. In an another study Krag *et. al.* (13) used peritumoral Tc 99 sulfur colloid. The over all identification rate was 93%. The accuracy of sentinel node in predicting axillary node status was 97%, the specificity was 100% and sensitivity was 89%.

Some authors (16,24,25) have used a combination of intraparenchymal / subdermal injection of blue dye and intraparenchymal radioactive tracer injection. Albertini *et. al.* (16) reports a detection rate of 92% and there was no false negative case in this study. Borgestin *et. al.* (22) reports a detection rate of 100% by using intradermal Tc labelled albumin. There was no false negative case in their study. The above results confirm the added benefits of the combination of both techniques for the overall success in mapping of sentinel node.

Table 1

Study	Technique	No. of Patients	Sentinel node identified	Detection rate	Sensitivity	Specificity	False -ve rate
Guiliano *et. al.* (5)	Blue dye	174	114	66%	88%	100%	11.9%
Guenthor (18)	Blue dye	145	103	71%	90%	100%	9.7%
Guiliano (17)	Blue dye	107	100	93%	100%	100%	0%
Flett (21)	Blue dye	68	56	82%	83%	100%	5%
Veronesi (15)	Subdermal radiocolloid	163	160	98%	95%	100%	4.7%
Borgestin (22)	Peritumoral radiocolloid	104	104	100%	100%	100%	1.7%
Krag (13)	Peritumoral radiocolloid	443	405	91%	89%	100%	11.4%
Crossin (23)	Peritumoral radiocolloid	50	42	84%	88%	100%	12.5%
Alex & Krag (19)	Peritumoral radiocolloid	70	50	71%	100%	100%	0%
Borgestin (24)	Intradermal blue dye + Peritumoral radiocolloid	25	25	100%	100%	100%	0%
Barnwell (25)	Peritumor blue dye + radiocolloid	42	38	90%	100%	100%	0%
Albertini (16)	Peritumor blue dye + radiocolloid	62	57	92%	100%	100%	0%
Cox *et. al.* (26)	Peritumor blue dye + radiocolloid	466	44	95%	–	–	–

Discussion

Nodal staging and predictive value of SLN biopsy in invasive breast cancer

For nodal staging and predictive value of SLN biopsy in invasive breast cancer, the standard of care has always included the pathological staging of clinically negative axilla since adjuvant therapies are available which unequivocally improve the disease free and over all survival in node positive patients. Before accepting SLN biopsy as a standard staging procedure, it must be established that it provides staging information as accurately as a standard axillary dissection. The critical issue here is the false negative rate. The standard axillary dissection (level 1 and 2) has a false negative rate of 2-3%, which is accepted to avoid morbidity of level 3 dissection. As can be seen in Table 1, the false negative rate in various series varies from 0%-12.5%. With increasing experience it is claimed that the false negative rate comes down (12). Studies have shown that a negative sentinel node has 95-100% likelihood of representing a clear axillary nodal basin. Thus it has a potential of avoiding dissection in a large number of patients without compromising the information regarding nodal staging.

To be of practical value, one has to rely on frozen section report of SLN in order to decide whether or not to proceed with axillary dissection. 10-17% of patients found to be negative on frozen section have subsequently turned out to be positive on permanent H & E staining or immunohistochemistry (12,15). Patients, therefore,

should be warned of this possibility to avoid distress, as these patients will require a formal axillary dissection.

As of today, there is no clear consensus about the indications of SLN biopsy. It is perhaps appropriate for stage T1 (2 cm) or T2 (2-5 cm) tumors with clinically negative axilla. As many as 75% of patients with T3 tumors have been shown to have positive SLN (26) and it may not be appropriate in these patients. However the upper limit is subject to debate. The procedure is applicable for patients undergoing either breast conservation or mastectomy. It is possible to perform the procedure after an excisional biopsy. Absolute contraindications include clinically palpable nodes, multifocal disease and prior major breast or axillary procedures that could interfere with lymphatic drainage (11).

Clinical relevance of micrometastasis

A sentinel node is found as only positive node in a high percentage (36-67%) of cases (5,15,16) as compared to previously reported 25% (27). Also in ductal carcinoma in situ up to 4.6% of patients have been found to have axillary metastasis (26) (usually <1%). This is because of more rigorous evaluation of sentinel nodes using multiple sections, immunohistochemistry and even PCR (5,15,26). The use of these techniques has increased the detection of occult metastasis resulting in up staging of the patients undergoing sentinel lymph node biopsy. Giuliano reported an increase in detection of axillary metastasis form 29% to 42% using multiple sections and immunohistochemistry (30).

Approximately 10% of patients may be up staged using immunohistochemistry (26). The biological significance of micro metastasis in SLNs has yet to be determined. However, from the data available from previous studies, it appears that they may have a prognostic significance (12). In a study where patients with negative axillary nodes on routine histology were reevaluated using multiple sections and immunohistochemistry, those with occult metastasis on reevaluation were found to have poorer prognosis compared with those who were confirmed to be tumor free on reevaluation (30). Thus sentinel node biopsy allows a more thorough evaluation by pathologists who can focus on 1-2 nodes rather than a complete axillary dissection sample. Detection of occult metastasis may also alter the management of patients by offering adjuvant treatment to those with positive nodes. However, one must bear in mind that before one says that a negative sentinel node means a negative axillary basin, all axillary nodes must be examined as thoroughly as the sentinel node. Longer follow up studies may clarify the correlation of occult metastasis in SLN to the rest of axilla and their biological significance.

Method of Identification

In the original procedure Giuliano *et. al.* (5) used a vital dye injection into the breast parenchyma to identify SLN. They reported a detection rate of 65.5%. With increasing experience their detection rate has increased to 93% (12). Others have reported similarly high detection rates (80-100%) using vital blue dye injection either into the breast parenchyma (21) or intradermally (24). An advantage of dye injections is that it is done a few minutes before the operation whereas lymphoscintigraphy must be carried out at least two hours before surgery. The drawback of blue dye study is that the axilla must be dissected blindly until the blue node is located. The advantage of radiocolloid injection and a hand held gamma probe is that it locates the node and it indicates exact site where skin incision should be made thus minimising the tissue disruption.

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