

Management of axillary lymph nodes in breast cancer patients in India: Axillary Lymph Node Dissection (ALND) vs. Sentinel Lymph Node Biopsy (SLNB).

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Abstract: Increased use of screening mammography, early detection of small tumours in breast cancer and the associated significant morbidity of ALND has led to the emergence of SLNB as a powerful tool in identifying a subset of node negative patients in whom the axilla is minimally disturbed. The same however, may not be feasible in an Indian scenario and therefore it may be recommended that Indian surgeons treating breast cancer should offer ALND for all invasive breast cancer patients routinely. Academic surgical divisions and dedicated high volume breast centers should initiate SLNB program for training and validation only, till the long term results of large western randomized trials are available.

Keywords: Breast cancer, Axillary lymph node dissection, Sentinel lymph node biopsy.

Introduction:

Surgery is the most effective and proven therapeutic intervention available for the treatment of breast cancer. Surgery was responsible for obtaining local control and long term disease free survival in more patients over the past century than any other treatment modality. Axillary lymph node dissection (ALND) became part of the accepted management of breast cancer in the mid 1800s, and continued to be the accepted standard of care well into the 1990s. Axillary lymph nodal involvement is still considered to be the single most important prognostic indicator in breast cancer patients^{1,2} and decisions about adjunct chemotherapy were weighted heavily by nodal status. This treated paradigm is shifting gradually, as the increasing use of screening mammography has resulted in the detection of very small tumors in the west with low probabilities of nodal involvement. In addition, significant morbidity is associated with ALND; 5 to 60% of patients experience some degree of side effects, including lymphedema of the arm, sensory numbness, and limitation of arm motion and strength³. Because of these developments, the acceptance of ALND as standard therapy for all breast cancer patients is diminishing in the west. Before abandoning ALND, however, several issues remain to be resolved, and are the subject of current intensive study. For clinically node-positive patients, recommendations are straightforward. Most practitioners agree that ALND remains important for loco-regional disease control, even if not necessary for adjuvant treatment decisions. In the case of clinically node-negative patients, however, there are additional issues. Is it appropriate to provide no treatment of the axilla? Is there a good alternative to ALND for the detection of occult nodal metastases? Sentinel lymph node biopsy (SLNB) is emerging as a powerful staging tool to identify the subset of node negative patients in whom an ALND and the attendant morbidity can be avoided⁴. The challenge today as we move closer to a selective approach to the axilla is to ensure that patients with positive nodes have those nodes identified and removed and patients with negative nodes experience minimal disturbance of axilla. However, there are other factors which can affect the breast cancer care adversely, especially in a country like India. The patient profile is different in India in comparison to the west and the general standards of surgical care of breast cancer are suboptimal. If the concept of SLNB is not well understood among the vast majority of Indian surgeons dealing with breast cancer, the potential for mismanagement are enormously high.

Need for ALND in Breast Cancer :

1. Staging
2. Prognostication
3. Therapeutic

Currently ALND is considered a gold standard as far as staging and prognostication of breast cancer patients is concerned^{1,2}. Whereas, the issue of therapeutic role of ALND is still a subject of debate.

The risk of providing 'No Axillary treatment':

The NSABP –B04⁵ study addressed the issue of therapeutic role of ALND and concluded that routine ALND does not contribute to survival. However, in a large review by Bland et al⁶ it has been shown that omission of ALND significantly decreases the survival in patients with invasive breast cancer. Recently, Kingsmore et al⁷ have shown that suboptimal axillary lymph nodal management significantly affects breast cancer survival. There are three groups of patients for whom the risk of nodal involvement is so low that ALND can be routinely avoided:

- patients with ductal carcinoma *in situ* (DCIS),
- patients with pure tubular carcinoma, and
- patients with microinvasive carcinoma.

Nodal metastasis is seen in less than 1% of cases with mammographically detected DCIS or pure tubular carcinoma <1 cm in diameter, and in about 3% of patients with microinvasive carcinoma. In a review by Singletary et al⁸, the incidence of nodal positivity ranged from 5 to 10% in patients with tumors 0–0.5 cm in size and from 10 to 20% in patients with tumors 0.6–1.0 cm in size. In patients with more 1 cm size the incidence of nodal involvement varies from 20 – 40% and in Locally advanced breast cancer patients 70 to 80 % have nodal involvement.

Relapse in Untreated and Treated Axilla:

The risk of axillary recurrence in untreated axilla varies from 10 to 40%^{6,7,9,10}. The risk is high in patients with T2 tumors, clinically palpable nodes and in patients showing LN invasion. There is a significant morbidity and increased mortality associated with axillary relapse. Whereas, axillary recurrence after axillary dissection is seen in less than 0-3% of patients^{6,8,11,12}.

Morbidity of ALND:

A significant number of patients experience post ALND morbidity; 5 to 60% experience some degree lymphedema of the arm, sensory numbness, and limitation of arm motion and strength^{3,8,13}. Incidence of lymphoedema varies from 5 to 50% in different

series depending on the criteria and method used for assessment of lymphedema. Combination of radiotherapy and surgery is a significant risk factor for development of lymphedema. However with the shift from radical to modified radical era and judicious use of radiotherapy, over all lymphedema rates have shown a decline in the 80s and 90s. Recent reported rates of post ALND lymphedema with out axillary irradiation ranges between 5- 10 %⁷.

Anatomical basis of ALND & Patterns of lymphatic Spread:

Three levels of lymph nodes (LN) are described in the axilla based on the relationship with pectoralis minor muscle. Anatomical studies have shown that Level –I harbors 75% of normal LNs and level II 20 % and level III 5%. Studies analyzing the pattern of spread of breast cancer reported a incidence of skip metastases to level III in the absence of level I or II LN metastases in less than 1% of patients¹¹. Chua et al¹⁴ reported an overall LN involvement of 45% in 308 operable breast cancers of which 78 % had involvement of level I only. Skip metastases to level I or II were noted in less than 1%.

Types/Variations of ALND:

1. Complete ALND- Dissection of Level I, II, and III nodes.
2. Level I & II ALND
3. Low Axillary Sampling – Removal of few level I nodes
4. Nerve sparing ALND
5. Sentinel Lymph Node Biopsy (SLNB)
6. Axilloscopic ALND

Based on the current evidence a complete ALND or Level I & II ALND is required to achieve optimum staging information and regional control in patients with invasive breast cancer (15). Axillary sampling and SLNB are good staging procedures. Axilloscopic ALND is still investigational. As per NSABP guidelines dissection of a minimum of 10 nodes is mandatory to avoid misclassification⁴.

Sentinel Lymph Node Biopsy (SLNB):

Sentinel lymph-node biopsy (SLNB) has been proposed as an alternative to routine ALND for the detection of occult lymph-node metastases in patients with clinically node-negative breast cancer. SLNB is based on the observation that specific areas of the breast drain by efferent lymphatics to a specific lymph node (‘sentinel’ lymph node – SLN), and then to other lymph nodes in the axilla. If the SLN is negative, the remaining lymph nodes are assumed also to be negative and no ALND is necessary. If the SLN is identified as positive by intra operative frozen section or imprint cytology, an ALND is carried out during the same surgery. If the SLN is identified as positive by more detailed histological or immunohistochemical techniques, an ALND can be carried out during a subsequent surgery.

The SLN is identified by injecting a vital dye (1% isosulfan blue) or a radioactive suspension (technetium sulfur colloid), into the breast parenchyma around the tumor^{16,17}. Some groups have also successfully used intradermal injections into the skin over the tumor and injections into the subareolar lymphatic plexus. The tracer can then be detected visually during surgery (when the dye is used) or by using hand held gamma probe while using radio active isotope.

To date, the results of SLNB have been impressive. The SLN can be identified in more than 90% of cases; of these, the SLN accurately predicts the status of the remaining lymph nodes in

more than 97% of cases. When the SLN is positive for metastatic disease, it is often the only affected node, especially in women with small primary tumors¹⁸. A trial from the American College of Surgeons is currently recruiting women who are SLN-positive by routine H&E staining to determine if completion ALND after SLNB will affect clinical outcome in this population. Can axillary lymph node treatment be safely eliminated in patients who are cytologically and histologically SLN-negative? Because of a significant frequency of false-negative results in SLNB, caution is urged in answering this question. False-negative rates reflect those cases in which the SLN was negative for metastasis even though there was histologically verified metastatic disease in the remaining axillary basin. In various studies the false negative-rate ranged from 1 to 11%¹⁸. Recent reports have associated high false-negative rates with increasing patient age, presence of medial tumors and the surgeon’s limited experience with SLNB. To gain further information about this issue, the NSABP B-32 is currently recruiting women who are pathologically SLN-negative to compare long-term locoregional recurrence rates in women who receive SLNB alone with those in women who receive SLNB followed by standard ALND. Recently Veronesi et al¹⁹ have published the results of SLNB alone in 953 SLN negative early breast cancer patients and showed a very low rate of axillary relapse.

IRCH – AIIMS Experience:

The feasibility of SLNB using Blue dye method along with intra operative imprint cytology was initiated as a validation study in the surgical oncology department of AIIMS and between 2000 and 2004, 250 node negative early breast cancers were included in the study. Over all accuracy of SLNB identification was 93 %, false negative rate was 8 % and accuracy of imprint cytology was 98 %. The preliminary work was published by Deo et al²⁰ in Asian Journal of Surgery. Currently we are not offering SLNB as therapeutic modality in breast cancer patients.

Pros and Cons of ALND & SLNB:

Advantages of ALND:

1. Time tested technique with proven efficacy.
2. Most accurate staging and prognostication tool
3. Evidence for therapeutic role available in node positive patients
4. Surgeon familiarity.
5. Very low risk of axillary relapse after ALND
6. Less patient apprehension as far as regional relapse is concerned

Disadvantages of ALND

1. High morbidity
2. Doubtful therapeutic role in node negative patients
3. Morbidity more than benefit in early node negative patients

Advantages of SLNB:

1. Accurate staging tool in node negative breast cancer patients
2. Proven technical feasibility & reproducibility
3. Minimal tissue dissection
4. Avoid ALND in SLN negative patients
5. Low incidence of lymphedema and arm morbidity
6. Limited tissue for detailed pathological evaluation

Disadvantages of SLNB:

1. SLNB role is mainly limited to node negative early breast cancers
2. Combination of techniques (dye and radio isotope) are required for accurate staging
3. Additional cost for the dye and gamma probe.

4. Need for Surgical training and validation.
5. Dedicated oncopathology divisions with frozen & cytology facilities are mandatory for SLNB program
6. High false negative SLN rate can lead to under treatment of patients
7. Long term oncologic out come in large randomized trials is yet to be proven

Indian Scenario:

Basically SLNB has evolved as an alternative staging tool for ALND in patients with node negative early breast cancer in the west. Seventy percent of breast cancer population in the west consist of screen detected node negative early breast cancer. This was possible because of the wide spread use of screening programs and public awareness campaigns held during the last three decades. Whereas, in India majority of breast cancer patients present with advanced stage disease and 60 to 70 % are node positive at presentation. We don't have a comprehensive screening program for early detection of breast cancer in India. Most of the breast cancer patients have no access to quality diagnostic and treatment facilities and currently primary level surgical mismanagement (under treatment) is prevalent in most parts of the country. Very few centers are following standard surgical guidelines. The media and physicians treating breast cancer should understand these issues and exercise caution before publicizing SLNB as a new surgical technique for managing breast cancer. If these relevant issues are not propagated by the Indian scientific community the potential for mismanagement of Indian breast cancer patients will be enormous.

In view of the issues discussed earlier, we would like to recommend that Indian surgeons treating breast cancer should offer ALND for all invasive breast cancer patients routinely. Academic surgical divisions and dedicated high volume breast centers should initiate SLNB program for training and validation only, till the long term results of large western randomized trials are available.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trials* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)