



Axillary sentinel lymph node biopsy: An overview

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ABSTRACT

The sentinel lymph node biopsy has become the standard procedure in the staging and management of axillary lymph nodes in early breast cancer. This procedure has been validated by several studies with an accuracy of 95% and a false-negative rate ranging from 5 to 15%.

Aim of this study is to analyze the most updated results and open problems reported in literature in the use of sentinel node biopsy in breast surgery.

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1. Introduction

Significant innovations in breast tumor surgery have involved the dissection of the axillary lymph nodes in the last few years. After results of validation studies, the sentinel lymph node biopsy (SLNB) instead of routine axillary dissection has quickly become the new standard of care in early breast cancer. The concept of conservation, which has been applied to the breast with the successful development of quadrantectomy, now also involves the axillary lymph nodes.

The histological status of the axillary lymph nodes is the most important prognostic factor in patients with breast cancer and it remains the most powerful predictor of recurrence and survival.

Early diagnosis of breast cancer has led to an increased number of dissections in which axillary nodes are free of disease. In this situation, a surgical technique that reduces the extent of the removed axillary tissue without losing prognostic information may have a very good impact on the quality of life.

The sentinel lymph node biopsy has proved to be a reliable alternative to the traditional axillary lymph node dissection with regard to predicting the histological status of the remaining lymph nodes in clinical T1/2 N0 breast cancers. The SLNB has the

advantage of reduced postoperative morbidity compared to the traditional axillary lymph node dissection.

2. Definition

The sentinel lymph node is the first regional step of lymphatic drainage and metastasis of a primary breast tumor. Although usually an axillary lymph node and most commonly in the central group of level I, the sentinel node may be of level II (behind the pectoralis minor muscle), level III (infraclavicular), an intramammary node, an intrapectoral (Rotter's) node or an internal mammary lymph node.

The rationale for the adoption of a sentinel node biopsy is that, due to the progressive involvement of axillary nodes by the tumor cells, the histology of the first lymph node would be representative of all the other axillary nodes.

3. Indications

The sentinel lymph node biopsy is indicated in patients with accreted diagnosis of ductal carcinoma and in patients with highly suspicious diagnosis of carcinoma when the clinical and imaging findings suggest that the lesion may be invasive. Patients who are undergoing a mastectomy for extensive or high-grade ductal carcinoma *in situ* or who have high probability of invasive carcinoma might also be considered for SLNB. More importantly, the patient should have a clinically negative axilla by palpation. The

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SLNB is mostly accurate for breast cancer of T1/2 stage, with a tumor measuring less than 3 cm of diameter.¹

4. Contraindications

4.1. Tumor size

Most early studies limited the use of SLNB to T1 or T2 tumors.² Although the incidence of lymph node metastasis increases with tumor size, the use of SLNB may be accurate in T2 and T3 tumors as well.³ Two studies indicate that there is no significant difference in the identification rate and false-negative rate in T3 tumors versus T1 tumors.⁴

4.2. Inflammatory breast cancer

There are insufficient data on women with inflammatory breast cancer to recommend the use of SLNB in this situation. The false-negative rate for patients with inflammatory breast cancer is unacceptably high so the SLNB is not recommended in this situation until more data are available.

4.3. Clinically positive axilla

Suspicious palpable adenopathy is a contraindication to SLNB. The lymphatics leading to these clinically positive lymph nodes may be blocked and prohibit accurate mapping leading to a false-negative result. When there are equivocal findings in the axilla, an ultrasound and fine needle aspiration may aid in the clinical decision-making obviating the need for SLNB when the lymph node is malignant.²

4.4. Neoadjuvant chemotherapy

Recently there have been many reports focusing on the accuracy of SLNB after neoadjuvant chemotherapy for advanced breast cancers. In a small institutional case series, the rate of SLNB identification after neoadjuvant chemotherapy has ranged from 85 to 96% and the false-negative rate has ranged from 0 to 33%.^{5,6} The largest study is a retrospective chart review of 2411 patients with operable breast cancers enrolled in the NSABP B-27 trial of preoperative chemotherapy. In this study, 420 patients underwent SLNB and of these, 340 patients had a complete axillary dissection. The sentinel lymph node was identified in 85% of 340 patients with a false-negative rate of 12%.⁷ Therefore SLNB can be proposed after neoadjuvant treatment in patients with T2/3 breast cancers without clinical or imaging evidence of nodal axillary involvement before chemotherapy.

4.5. Multicentric disease

More recently, several suggested techniques have been proposed to perform SLNB in this setting of patients. Subdermal, intradermal and subareolar routes of tracer injection are associated with greater success with a comparable false-negative rate. Several small nonrandomized series in which such an approach was evaluated have demonstrated that the performance of SLNB is similar to that for women with focal disease. Studies with larger patient populations are indeed necessary.^{8,9}

4.6. Ductal carcinoma in situ

The use of SLNB in ductal carcinoma *in situ* (DCIS) is still controversial. DCIS by definition has little or no metastatic potential and recurrence is quite low after adequate conservative

surgery. The SLNB may be appropriate in DCIS with foci of microinvasion, defined as those with a palpable mass, mammographic mass, histology suspicious but not diagnostic, multicentric disease that required a mastectomy, or histology with high nuclear grade.¹⁰

4.7. Prior breast or axillary surgery

The impact of prior breast or axillary surgery has not been well characterized. Limited data suggest that a previous excisional biopsy does not affect the success of SLNB.¹¹ It is likely that more extensive breast surgery such as mastoplasty would be associated with a higher false-negative rate. Although data suggest that SLNB may be proposed in women who have had axillary surgery, the success rate is likely to be lower.¹² Therefore SLNB is not recommended in the setting of prior axillary surgery.

4.8. Pregnancy

Vital dyes should not be administered to pregnant women, however radiolabeled colloid is proven to be safe because the dose of radiation to the fetus is minimal.

5. The sentinel lymph node biopsy technique

The techniques to identify the sentinel axillary node in breast cancer involve the use of technetium sulfur colloid and isosulfan blue dye in the USA, and technetium-labeled albumin and patent blue dye in Europe. The utilization of both radiocolloid and blue dye increases recognition of the sentinel lymph nodes. Individual surgeons and institutions may utilize either radiocolloid or blue dye alone with equal success after appropriate training and experience. Several different sites of injection of radiocolloid and/or blue are currently in use: peritumoral, intratumoral, subcutaneous, intradermal, and subareolar. The best success consists of injecting the radiocolloid/blue dye in the subdermis above the tumor or in the tissue immediately surrounding it. In cases where a previous biopsy was performed, the radiotracer is injected in the original area. The procedure consists of using varying doses of the radiolabeled colloid, from 0.1 (3.7 MBq) to 3 milliCurie (mCi) (111 MBq), in varying volumes of saline, from 0.1 to 5 ml. Close cooperation between the nuclear medicine department and the surgeon is necessary and recommended. Mammary and axillary lymphoscintigraphy are taken after 30 min up to 2–4 h after injection. The interval between injection of radiocolloid and the operation also varies, from 2 h to a full 24 h day before surgery is undertaken.

When blue dye is used, the mean volume is 3–4 ml. The time between the injection and the axillary incision also varies, depending upon patient size and the location of the tumor in the breast.

A small incision of 1.5–2 cm is sufficient to explore the axilla with the probe which is in the proximity of the sentinel node that gives out a recognizable acoustic signal. Removal of the sentinel lymph node may be often obtained through the same incision made for the removal of the primary breast carcinoma, especially if it lies in the upper outer quadrants.

It is important to differentiate 'failed' and 'false-negative' terminology with regard to SLNB. The latter term defines the identification of sentinel nodes that are intraoperatively negative but, upon further final pathology exam of the processed lymphoid material, they contain metastatic disease. 'Failed' SLNB implies the inability to identify the sentinel lymph nodes. The 'failed' SLNB usually leads to an immediate traditional axillary node dissection.

The radiation exposure to patients, surgeons, operating room personnel and the staff of the pathology and nuclear medicine

departments from radiocolloid sentinel node techniques is extremely low.

6. Pathology

In response to SLNB, new surgical pathology protocols have emerged to ensure that the intraoperative examination of the sentinel lymph node is as accurate as possible. Recently, added to the routine hematoxylin and eosin staining of lymph nodes has been the additional examination of the lymph nodes by cytokeratin immunohistochemistry (IHC) staining or polymerase chain reactions. These techniques may assist in detecting single malignant cells or few foci of tumor clusters. Each sentinel node is measured and cut along its longitudinal axis into sections of 1.5–2 mm of thickness. The lymph node sections are then entirely submitted in formalin for paraffin section histology. The immunohistochemical technique should not be considered standard practice (even if few USA pathology departments do it routinely), but may be performed when the hematoxylin and eosin stained slides have suspicious cells that are equivocal.

7. Review of relevant literature

Initial results on SLNB in breast carcinoma and many later studies indicated that this is a reliable axillary staging technique. The reported accuracy ranges from 90 to 95% and false-negative rates range from 5 to 15% even if the goal for false-negative should be <5%. To date, only one prospective randomized clinical trial has been published.¹³ Veronesi et al. randomly assigned 516 patients with tumors of 2 cm or less to either SLNB and axillary dissection or SLNB followed by axillary dissection, only if the SLN contained metastases. For the patients who had SLNB and axillary dissection, the false-negative rate was 8.8%. There were fewer axillary complications and less morbidity in the group that had axillary dissection only if SLN was positive for disease. For patients who did not have axillary dissection, there were no axillary recurrences and the short-term survival was the same as for the patients with tumor-free lymph nodes who had axillary dissection. Three large randomized trials on SLNB are currently ongoing.

The ALMANAC trial, begun in November 1999, is a randomized multicenter trial in the UK comparing SLNB with conventional axillary dissection in clinically node-negative patients. In total, 1031 patients have been randomized. The authors concluded that SLNB is associated with less arm morbidity and a better quality of life and is cost-effective compared with standard axillary treatment.

The second trial is named NSABP-32 and is a phase III, randomized trial which compares axillary resection with SLNB, involving more than 5000 patients in North America. It began in 1999 and no preliminary results have been published as of yet.

The third trial, RACS SNAC, is a multicenter randomized trial of the Royal Australian College of Surgeons, which recruited 789 women.

The recently reported meta-analysis demonstrates that, among patients with positive SLN, 48.3% were found to have additional node disease in axillar nodal dissection.^{12–14} Thus, routine axillary dissection is recommended for patients with a positive SLN. More problematic is the management of patients for whom the SLN is positive only with the use of special studies, such as the immunohistochemical (IHC) staining with antibodies to cytokeratins. IHC analysis can upstage disease for approximately 10% of patients who have a negative SLN. In the new American Joint Cancer Commission (AJCC) staging system, the node classification is not clinically altered by clusters of isolated tumor cells of 0.2 mm or less. It remains unclear if isolated tumor cells or micrometastases (lymph node metastases of more than 0.2 mm but not larger than 2 mm)

detected with hematoxylin and eosin staining or immunostains, represent an adverse prognostic factor and whether axillary dissection should be performed in all such cases. However, metastasis is found in nonsentinel lymph nodes in approximately 10% of patients with isolated tumor cells in the SLN and in 20–35% of patients with micrometastases in the SLN. Until further studies addressing the clinical relevance of isolated tumor cells or micrometastases are complete, it is recommended that routine axillary dissection for patients with micrometastases (>0.2 mm and <2 mm) found on SLNB is completed.

To solve the problem of false-negative SLN on the ordinary frozen section procedure, Veronesi et al. have proposed two solutions.¹³ The first is to have a complete examination of the sentinel lymph node intraoperatively with a technique extensively in use at the European Institute of Oncology. This technique consists of a large series of sections at 50 µm intervals, so that all the node is exhaustively examined without the risk of micrometastases escaping the histologic examination. This method is time-consuming and expensive, but the avoidance of a second operation in 20% of the cases largely compensates for extra costs. The second solution proposed by Veronesi et al. is to perform the sentinel node biopsy under local anaesthesia on an outpatient basis a few days before the final surgery.¹⁵ If the sentinel node is negative, surgery will be limited to breast lumpectomy/quadrantectomy, again on an outpatient basis, or to a mastectomy; if the sentinel node is positive, the final surgery will include total axillary node dissection.

8. Conclusion

Sentinel lymph node biopsy has been widely accepted as a standard procedure for the staging and management of early breast cancer.^{15–22} A routine sentinel lymph node process needs a high level of competence and a sufficient training program among members of the surgery department, nuclear medicine and pathology department. Many practical problems remain and details of the technique are not yet standardized. Ongoing large clinical trials will hopefully provide answers regarding numerous problems in the near future.

Conflict of interest

None declared.

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Ethical approval

None.

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