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Review

Sentinel lymph node biopsy indications and controversies in breast cancer

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ABSTRACT

Sentinel lymph node biopsy (SLNB) has become the standard of care for early breast cancer. Its use in breast cancer has been evaluated in several randomized controlled trials and validated in multiple prospective studies. Additionally, it has been verified that SLNB has decreased morbidity when compared to axillary lymph node dissection (ALND). The technique used to perform sentinel lymph node mapping was also evaluated in multiple studies and the accuracy rate increases when radiocolloid and blue dye are used in combination. As SLNB became more accepted, contraindications were delineated and are still debated. Patients who have clinically positive lymph nodes or core biopsy-proven positive lymph nodes should not have SLNB, but should have an ALND as their staging procedure. The safety of SLNB in pregnant patients is not fully established. However, patients with multifocal or multicentric breast cancer and patients having neoadjuvant chemotherapy are considered candidates for SLNB. However, the details of which specific neoadjuvant patients should have SLNB are currently being evaluated in a randomized controlled trial. Patients with ductal carcinoma in situ (DCIS) benefit from SLNB when mastectomy is planned and when there is a high clinical suspicion of invasion. With the advent of SLNB, pathologic review of breast cancer lymph nodes has evolved. The significance of occult metastasis in SLNB patients is currently being debated. Additionally, the most controversial subject with regards to SLNB is determining which patients with positive SLNs benefit from further axillary dissection.

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Lymph node status in breast cancer patients remains one of the most important prognostic factors. Lymphatic mapping and sentinel lymph node biopsy (SLNB) has now virtually replaced axillary lymph node dissection (ALND) for axillary staging in clinically node negative patients. The landmark studies by Giuliano applied techniques for lymph node mapping used in melanoma patients to breast cancer patients [1–3]. The use of SLNB is now widely accepted and considered standard of care for early breast cancer patients. However, despite its introduction over 15 years ago, there are still controversies regarding SLNB and axillary dissection which are currently being debated.

There have been many prospective studies supporting the use of SLNB in breast cancer but interestingly, few randomized controlled trials to validate its use. However, with these randomized controlled trials and validation studies there is more than sufficient evidence to show its effectiveness in the appropriate patient. One of the earliest randomized trials was by Veronesi's group [4–6]. From 1998 to 1999, 516 breast cancer patients were randomized to SLNB followed by ALND or SLNB followed by ALND only if the sentinel node contained metastases. Patients had tumors less than 2 cm and underwent breast conserving surgery only. The ten year results were recently published; there was no difference between ipsilateral breast recurrence, axillary recurrence, and distant recurrence between the two groups. The 10-year breast cancer-related event-free survival was 88.8% (95%CI: 84.6–92.9%) for the ALND group and 89.9% (95%CI: 85.9–93.9%) in the SLNB group. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial was a randomized controlled Phase III trial at 80 centers in the United States and Canada comparing SLNB followed by ALND to SLNB followed

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by ALND for only those with positive sentinel lymph nodes (SLN) [7,8]. Patients were enrolled from 1999 to 2004 and only patients with clinically negative nodes were eligible. Patients were stratified based on patient tumor size, age and type of breast surgery. The accuracy rate overall was found to be 97% with a 9.8% false negative rate. Overall survival (OS), disease free survival (DFS), and regional control were equivalent between the two patient groups, concluding that SLNB is an appropriate, safe, and effective therapy. The Sentinella/GIVOM trial published by Zavagno et al. combined 18 clinical centers with a variety of settings and included patients with tumors less than 3 cm [9]. Patients were randomized to either receive a SLNB followed by an ALND or SLNB followed by ALND only in the patients with SLN metastasis. The study was designed to compare OS between the groups. The OS was slightly higher in the ALND arm having 89.9% 5-year survival compared to 87.6% in the SLNB arm, but did not reach statistical significance. The identification rate of the SLN was high at 95%, but the false negative rate was also high at 16.7%. The false negative rate in this trial was attributed to the variety of centers with both academic and community hospitals included, as well as concerns for some of the participating surgeons having limited experience in breast cancer surgery.

There have been many prospective trials that have validated the use of SLNB in breast cancer. Krag et al. evaluated the technique of SLNB in 443 patients with breast cancer from 1995 to 1997 [10]. This multicenter validation study demonstrated varying false negative rates depending upon individual surgeons. For the patients in whom a SLN was detected, the overall accuracy for detection of metastatic disease was 96.8%. In the validation study by Giuliano et al., SLNB followed by ALND was performed in 107 consecutive patients with breast carcinoma from 1994 to 1995 [11]. SLNs were identified by the use of blue dye only with an identification rate of 93.5%. Veronesi et al. evaluated 163 consecutive breast cancer patients. All the patients had a SLNB with the use of radioisotope injection for lymphatic mapping, followed by an ALND [12]. Accurate prediction of axillary lymph node status occurred in 97.5% of the patients where the SLN was found and in all cases where the primary tumor was less than 1.5 cm. In 38% of the patients found to have axillary metastasis, the SLN was the only positive lymph node. In a systematic review of 68 studies from both pre- and post- SLN era, a pooled axillary recurrence rate of 0.6% was found in negative sentinel node patients [13]. The study also showed no benefit to ALND after a negative SLNB.

The literature has described various techniques to identify the SLN. It has been shown by Beitsch et al. that subareolar injection yields were higher than with peritumoral injection [14] For lymphatic mapping, there is variation regarding the agent used. In the meta-analysis by Kim et al., 18 studies used blue dye only, 16 studies used radiocolloid alone and 34 used a combination [15]. The false negative rate was lowest in the combination group (7.0%) as compared to 8.8% for radiocolloid alone and 10.9% for blue dye alone. In the study by Cox et al., the two different lymphatic mapping methods were evaluated [16]. With blue dye only, the SLN identification rate was 80.3% as compared to an 88.6% identification rate with radiocolloid. Using a combined technique, the identification rate was 95.7%. Although the identification rate is higher and false negative rate is lower using both mapping techniques together, there is no consensus regarding which technique should be employed.

Additionally, many studies have reported decreased morbidity after SLNB compared to ALND. Veronesi et al. reported decreased arm mobility, increased pain and increased lymphedema rates in the ALND group, as compared to the SLNB group [4]. The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial, a randomized control trial, reported less arm and shoulder morbidity and overall better quality of life in the SLNB group compared to patients undergoing ALND [17,18]. The risk of lymphedema was 5–7% and sensory loss was 8.7–11% in the SLNB group compared to 13–14% and 19–31%, respectively in the ALND group. The American College of Surgeons Oncology Group (ACOSOG) Z0010 was a prospective, multicenter trial in which one of the secondary endpoints involved surgical complications after SLNB [19]. It was found that increasing age (≥70) and increasing number of SLNs removed (≥5) were associated with an increased risk of postoperative axillary seroma. At 6 months from the time of surgery, 8.6% of patients reported axillary parathesias, 3.8% had a decrease in arm range of motion, and 6.9% had proximal upper extremity lymphedema. Significant factors predicting postoperative lymphedema was increasing age and increasing body mass index (BMI).

Sentinel lymph node biopsy is controversial or contraindicated in certain patient populations. Patients who have biopsy-proven axillary lymph node metastasis or have clinically positive nodes should have ALND as their initial procedure. For pregnant patients, blue dye is considered to be unsafe and is not an option. Regarding radiocolloid in pregnant patients, its use is not recommended prior to 30 weeks gestation as there is limited data with regards to the radiation dose to the fetus, although studies have proposed a low risk to the fetus [20–25]. The National Comprehensive Cancer Network (NCCN) guidelines [26] state that there is insufficient evidence data on which to base recommendations and the use of SLNB in pregnancy should be individualized. Concerns have also been raised with regards to patients who have had previous breast surgery. Port et al. at Memorial Sloan-Kettering Cancer Center (MSKCC) evaluated patients who had previous breast or axillary surgery at their institution [27,28]. They found that the SLN was identified 55–75% of the time with a likelihood of success in finding the SLN was found to be increased when less than 10 nodes were previously removed. There were no false negative rates reported, but most patients did not go on to full ALND; there were no axillary recurrences at 2 years. Additional concerns were raised regarding patients with multifocal breast cancer. In terms of lymphatic mapping of these patients, there have been multiple studies showing evaluating the accuracy in patients with multiple tumor sites in the breast. Jin Kim et al. mapped each tumors separately, one with blue dye and the other with isotope, and found that the lymphatic drainage of the tumors coincided with drainage of the whole breast: all patients had uptake of both blue dye and isotope in at least one SLN [29]. An additional study by Kim et al. looked at multicentric and multifocal breast cancer patients compared to patients with unifocal disease [30]. They reported a SLN accuracy rate in patients with multiple tumors of 98.0% with a false negative rate of 8.6%, which was comparable to patients with single tumors.

In patients with ductal carcinoma in situ (DCIS), there is controversy over which of these patients would benefit from a SLNB. A retrospective study of 587 patients with DCIS was performed by Goyal et al. In this study, 38% of the patients were found to have invasive disease on final pathology [31]. Multivariate analysis revealed that a mass on clinical exam or a mass on mammogram were significant independent predictors of invasive disease on final pathology. Of the patients evaluated, 269 had axillary assessment at initial surgery, with 13% of these patients having axillary metastasis. All of these patients were found to have invasive disease on final pathology. In another recent retrospective review of 110 DCIS patients, the rate of invasive cancer at surgical pathology evaluation was found to be 13.6%, and 93% of these patients had high grade DCIS by core needle biopsy [32]. The authors from both of these studies recommended use of SLNB in patients where high clinical suspicion of invasive cancer exists, such as those with a palpable mass, and further recommend performing a SLNB on DCIS patients when a mastectomy is to being performed as this will preclude future SLNB if invasive disease is found on final pathology.

When SLNB came to the forefront, there was debate regarding the qualifications required to perform the procedure, primarily