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Sentinel Lymph Node Biopsy for Breast Cancer: Our Technique and Future Directions in Lymph Node Staging

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Abstract

Breast cancer remains a major cause of cancer death for women in the United States. Accurate cancer staging, especially of the axillary lymph nodes, is essential for predicting the prognosis of patients and for determining the appropriate multimodality treatment strategy. Historically, the traditional approach for staging the lymphatic metastasis in breast cancer has been Axillary lymph node dissection (ALND). However, as the understanding of the lymphatic drainage of the breast has improved, the Sentinel lymph node (SLN) biopsy has replaced ALND as the gold standard for lymph node staging in breast cancer. Multiple studies have demonstrated the benefits of SLN biopsy compared to ALND in terms of morbidity, while maintaining the clinical ability to appropriately stage patients, but without any loss in therapeutic impact. In this review, we discuss the historical development of SLN biopsy, describe our technique in detail, and discuss the possible future directions of the lymphatic staging of breast cancer.

Introduction

Breast cancer is the second leading cause of cancer death and affects one in eight U.S. women in their lifetime [1]. When patients are diagnosed with breast cancer, they are grouped by prognosis following the American Joint Committee on Cancer (AJCC) staging system, which also helps guide the treatment plan. Breast cancer staging is based upon the progression of the disease from a tumor in the breast that invades surrounding tissue and spreads through a process as metastasis to the lymph nodes in the axilla and then to the distant organs such as the brain, bones, lung, or liver [2]. The AJCC staging system evaluates tumor size and extent of tumor invasion, the presence and location of lymph node metastasis, and distant organ metastasis, and correlates these characteristics with survival data to produce a prognostic staging category for the patient [3]. In addition, data by prognostic stage on the efficacy of surgery, radiation, hormonal and chemotherapy to improve survival help guide clinicians and patients on the appropriate therapeutic strategy [2].

The axillary lymph nodes are staged to aid in determining both the stage and the appropriate therapy of patients [2]. In fact, the status of the axillary lymph node is the most important predictor of outcome in breast cancer [2,3]. When breast cancer patients present with palpable axillary lymph nodes that are suspicious for cancer metastases, these patients are staged clinically according to the AJCC system. However, when a breast cancer patient has no clinically suspicious axillary lymph nodes, the lymph node stage of the patient is in question. Historically, the axillary lymph nodes were surgically removed by performing an axillary lymph node dissection or axillary lymphadenectomy (ALND) [4]. This procedure entails surgically removing all of the lymph nodes in the axilla by carefully dissecting the lymph nodes off of the surrounding blood vessels, muscles and nerves which control the muscles of the shoulder. Aside from the risk of injuring these structures, because the lymph nodes in the axilla not only drain the breast, but also the upper extremity, there is a risk of swelling in the arm, known as lymphedema after lymph node dissection [4]. Despite such morbidity, ALND has been pursued because of the importance of lymph node staging in breast cancer. In order to minimize these complications, surgical oncologists developed a method to evaluate the axillary lymph nodes for cancer spread without having to remove all of the lymph nodes, a staging surgical procedure known as a sentinel lymph node (SLN) biopsy. In this review, we will discuss the historical development of SLN biopsy, our technique, and future directions in lymph node staging.

Development of Sentinel Lymph Node Biopsy

The idea of a sentinel lymph node, which is the first node in the draining lymph node basin to receive cancer metastasis, was described in 1951 during a total parotidectomy [4,5]. Twenty years later, descriptions of the drainage of contrast medium in breast lymphatic vessels demonstrated flow to an isolated lymph node first, and then subsequent drainage through many lymphatic channels to the other lymph nodes [4,6-8]. This first draining lymph node acted as a sentinel for the breast receiving metastasis before the other lymph nodes in the axilla. By the early 1990's, a surgical procedure was developed to identify the SLN, remove it, and microscopically examine the lymph node to determine if it contains metastatic breast cancer to determine if the patient should have the remaining lymph nodes removed [4,9-11].

Studies have utilized SLN biopsy and compared its ability to correctly identify that a patient had breast cancer lymph node metastasis against the results of ALND. It has been reported to successfully identify the SLN in 92% to 98% of patients, with a 97.5% - 100% agreement with ALND, and a 97.5% - 100% concordance between SLN biopsy and ALND [12-17]. An initial study by Veronesi et al. [17] attempted SLN biopsy in 376 patients followed by axillary lymph node dissection. The study reported successful identification of the SLN in 371 of those patients. Importantly, it also demonstrated that the SLN accurately predicted whether the remaining lymph nodes were positive for disease in 95.5% of those patients, with a false negative rate of only 6.7%. In

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addition to this initial study it has been shown that the chances of SLN biopsy falsely staging a patient with lymph node metastasis as being without such disease was evaluated and reported to range from 0% - 15% (mean of 8.8%), depending partially on surgeon experience and breast tumor characteristics [18]. A national trial (National Surgical Adjuvant Breast and Bowel Project (NSABP)-B32) was conducted to evaluate the safety and efficacy of SLN biopsy as the gold standard for lymph node staging by randomizing 5,611 patients, and once again the above findings of accuracy and technical success were validated with similar outcomes [19].

Our Sentinel Lymph Node Biopsy Technique

The procedure can be divided into 2 portions; mapping and harvesting of the SLN. For mapping, we use 1 mCi of Technitium-99m sulfur colloid in 0.5ml normal saline, and isosulfan blue dye (Lymphazurin 1%, US Surgical Corp, Norwalk CT). In the U.S. technetium-99m sulfur colloid is the most widely used compound, as opposed to technetium-99m colloidal albumin which is mostly commonly used compound in Europe. In our institution, the surgeon injects the radioisotope him/herself at the "preoperative holding area" prior to the procedure, which allows for the most accurate timing from the time of injection and the detection of SLN during the operation using a hand-held gamma probe. It has been the author's experience that when the timing is too early, the radioisotope count in the SLN will be very low and its detection from the skin surface will be difficult, and when the timing of injection is too late, the radioisotope may diffuse to the non-sentinel lymph nodes that make detection of true SLN difficult with high "background noise". The author injects 0.3ml (0.6 mCi) of radioisotope in the subareolar dermis, and 0.2ml (0.4 mCi) in the dermis above the tumor, a minimum of 1 hour to maximum of 2 hours prior to the time of probing during the operation. This is based upon the physiology of mammary lymphatics that nearly all breast tissue lymphatic drainage passes through the subareolar plexus of Sappey and then into the axillary nodal basin. We use a 1ml tuberculin syringe with either a 27 gauge or a 30 gauge needle to minimize patient discomfort; however, they often complain of a burning sensation. After the patient is induced with anesthesia and prepared and draped in a sterile manner for surgery, isosulfan blue dye is injected in the same manner. The author commonly waits for a minimum of 5 to 10 minutes prior to incising the skin. The major risk of isosulfan blue dye is the risk of allergic/anaphylactic reaction, which can occur in one out of 1000 patients treated. An alternative option for the dye will be methylene blue, which has been reported to have similar SLN identification rates, lower cost, and a lower risk of allergic reaction. The risks of methylene blue are necrosis of the skin and dermolysis when it is inadvertently injected into the dermis, and is highly teratogenicity.

The incision is usually made in the lowest skin crease in the axilla, which is often where a hand-held gamma probe will detect high signal to mark where to make the incision. One of the tips to effectively identify the SLN is to aim the probe away from the nipple to avoid picking up the signal from the injection site and breast tissue. The author utilizes the probe in every step of this procedure to have a 3-demension image of the location of the SLN from the skin surface level. After skin incision and the subcutaneous fat is encountered, the author utilizes a brunt dissection technique with a tonsil cramp and Army-Navy retractor to avoid disruption of lymphatic vessels. The appropriate direction of dissection is confirmed using the probe each time the cramp is used to dissect. Often times a blue stained lymphatic vessel is encountered, which leads the dissection to the SLN, which will also appear blue. The surrounding lymphatic vessels are either tied or clipped to excise the SLN. After the hot SLN is excised, the radioisotope count of the SLN will be quantified *ex vivo*. Exploration is completed when the remaining count in the axilla is 10% or less than the count of the hottest excised SLN. The author closes the surgical wound in a usual fashion with 3-0 vicryl sutures for the dermis and 4-0 monocryl for the skin without drain placement.

Which Patients Would Benefit From Sentinel Lymph Node Biopsy?

Although it had been demonstrated that SLN biopsy adequately identifies which patients have lymph node metastasis, the question remained whether performing the more extensive traditional ALND instead of the less invasive SLN biopsy provided cancer patients with a better therapeutic outcome. Therefore, a multicenter randomized phase III trial was performed which randomly assigned 5,611 patients to SLN biopsy and ALND or to SLN biopsy and ALND only if the SLN biopsy had been positive for metastatic breast cancer. The results from that study demonstrated no significant difference in disease free survival, regional control, or overall survival which was 91% v. 90.3% for SLN+ALND v. SLN+ALND only if the SLN biopsy was positive [15]. Another study from a single center evaluated 5 year disease free survival of 532 patients with T1 breast cancer (tumor ≤ 2cm) who were randomized to either SLN biopsy followed by ALND if it had been positive or SLN biopsy alone. The results demonstrated that there was no significant difference in disease free survival, which was 92.9% v. 88.9% for SLN+ALND v. SLN alone, respectively [20]. The results of this trial suggest that sentinel lymph node biopsy has no therapeutic impact on breast cancer survival.

Studies have evaluated which patients would benefit the most from SLN biopsy. In general, SLN biopsy has been selected for patients with T1 (tumor ≤ 2cm) and T2 (tumor >2cm - ≤ 5cm) disease, without evidence of multifocal involvement or clinically positive lymph nodes [19]. Studies have also evaluated whether SLN biopsy produces less of the morbidity potentially associated with the traditional ALND by evaluating quality life years and arm function after each procedure. A trial which randomized over a thousand patients demonstrated that SLN biopsy alone compared to SLN biopsy combined with ALND resulted in improved quality of life and arm function [21]. However, the question remained whether ALND is still necessary even when the SLN biopsy is positive for lymph node metastasis.

Because of the strong results produced from studying SLN biopsy, many clinicians began to question whether there was any role for ALND. American College of Surgeons Oncology Group Z0011, a multicenter, randomized clinical trial conducted by Giuliano et al, evaluated whether a positive SLN biopsy necessitates ALND in order to improve overall survival in breast cancer patients [22]. In order to reach statistical power to be able to determine non-inferiority, this trial had planned to randomize 1,900 patients with one or two positive SLNs to either ALND or no further surgical treatment, with all patients receiving appropriate radiation and systemic therapy. However, the study was published after enrollment of only 891 patients for randomization. After following these patients for a median of 6.3 years, 5 year overall survival was 91.8% versus 92.5%, and 5 year disease free survival was 82.2% versus 83.9%, for ALND versus SLN biopsy alone, respectively [22]. With no statistical difference between the two groups, some conclude that additional ALND is no longer necessary for SLN biopsy positive patients, but others argue that the number of patients studied in this trial was not statistically sufficient to produce generalizable findings.

Another limitation of this study is that 82% of the patients had estrogen receptor positive tumors which are known to have better survival than estrogen receptor negative tumors. Because less aggressive surgical treatments (i.e. no ALND) were applied in this study, there is a possibility for a bias for more aggressive and intense chemotherapeutic regimens were performed. Further, since all the patients who participated in this trial received adjuvant irradiation to the axilla some argue that the results may change if a patient is not to receive those treatments. Based on these results, the medical necessity of ALND continues to be called into question when patients have positive SLN biopsy. However, because of the questions of bias, statistical power, and the distribution of tumor types, it is difficult to draw strong conclusions of general applicability to breast cancer patients.

At our institution, immunohistochemistry is not utilized as a modality to identify micrometastatic disease in order to inform the decision of whether to proceed with ALND after SLN biopsy. Because circulating tumor cells are known to be present throughout the body in patients with breast cancer (approximately 1 – 10 cancer cells per milliliter of blood). micormetastatic disease appears to be more consistent with these circulating tumor cells and thus removing the remaining axillary lymph nodes while the patient has these same cells circulating throughout their body is felt to provide no therapeutic benefit [26]. Furthermore, since circulating tumor cells detected by immunohistochemistry alone can be found in virtually all breast cancer patients regardless of stage, removing more lymph nodes with only such micrometastatic disease would not provide any diagnostic benefit either.

Although it has been shown that SLN biopsy reduces the morbidity associated with ALND, it does not eliminate it entirely. Accordingly, there has been an attempt to determine which patients who currently meet criteria for lymph node staging might not require a SLN biopsy either. Specifically, the question has been which patients have a sufficiently low probability of lymph node metastasis that it would be safer to not expose them to the risks of SLN biopsy. There have been no prospective randomized trials to evaluate this question, but there have been single institution retrospective reviews which have sought to estimate what the risk is for lymph node metastasis for patients with a small tumor.

Some single institution series have demonstrated that patients with T1a tumors (size 1mm – 5mm) had a SLN biopsy positive rate of 9% - 16% [23,24]. In another single institution series the rate of positive SLN biopsy also in patients with T1a tumors was demonstrated to be only 2% [25]. However, these studies provided no information on the effect of never staging the lymph nodes in this patient population. On the face of these results, there are those who argue that SLN biopsy might not be required in this patient population. However, because of the limitations of these single institution series the results are not generally applicable. In fact, because the axillary node status remains the most important predictor of outcome in breast cancer patients, and the data from these studies are limited, there have been no recommendations to omit axillary lymph node staging in breast cancer.

Conclusions

SLN biopsy is a well accepted technique which is now the gold standard for axillary lymph node staging for breast cancer, without any therapeutic impact on outcome. Controversy remains regarding whether or not to perform a full ALND on a patient who was found to have lymph node metastasis by SLN biopsy. Because of the importance of lymph node status to appropriately staging and guiding treatment in breast cancer, currently there are no recommendations to omit SLN biospy. As further studies continue to gain a greater understanding of this disease, recommendations will evolve regarding the appropriate staging and treatment strategies for these patients.

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