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Sentinel Lymph Node Biopsy in Breast Cancer: A Work in Progress

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Abstract

The sentinel lymph node biopsy is a safe, accurate operation for the initial staging of breast cancer. Over the last decade, there has been increasing literature supporting its use, and it is now considered a standard of care for the initial evaluation of metastatic spread to the axillary lymph node chain.

Keywords

Sentinel Lymph Node; Breast Cancer

Introduction

The status of the axillary lymph nodes is one of the strongest prognostic factors in women with early stage breast cancer, and the sentinel lymph node biopsy (SLNB) has become the standard of care in the assessment of metastatic spread to the lymph node basin.^{1, 2} By definition, the sentinel lymph node is frequently the first node in the lymphatic basin that receives drainage from an anatomic region and is immunologically responsible for that region.³ Its relatively low false negative rate of 5 to 10% and high sensitivity rate of 90 to 95% in the detection of cancer to the lymph node basin has made this minimally invasive operation a standard.^{4, 5} The sentinel node biopsy (SLNB) has transformed the surgical management of early breast cancer and although it is now the standard of care we continue to explore the utility of the procedure in more controversial areas such as post neoadjuvant therapy, explore information about the host response to cancer, and test new refined reagents to better identify lymph nodes with metastatic cancer as well.

Historically, the concept of a mapping lymphatic drainage began in the 1950s.⁶ By the 1970s, it was noticed that some nodes received drainage before others and were termed, the “sentinel node.”⁷ Lymphatic mapping with the purpose of discovering the sentinel node was first described in 1992 for cutaneous melanoma with the use of blue dye by the late Donald Morton.⁸ Krag et al. then applied sentinel lymph node mapping with injected radiotracer using the gamma probe in the treatment of breast cancer in 1993.⁹ In the molecular level, the

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mechanism that determines sentinel lymph node status involves antigen presenting cells and their ability to uptake macromolecular tracers.³ Presently, SLNB has become the standard over the axillary lymph node dissection (ALND) in the staging of the axilla for clinically node negative disease because of its accuracy and limited morbidity and invasiveness.¹⁰

Immune response to the Sentinel Lymph Node in the Setting of Breast Cancer

Much in the way of studying the immune response in a sentinel lymph node closest to the cancer has led to the findings that breast cancers and melanomas have the ability to down regulate a host's immune response in the lymph node. The anti-tumor immune functions of the lymph node are blunted by the cancer's ability to suppress the immune system because of cancer derived cytokines, prostaglandins, gangliosides, and lipoprotein antigens that are transmitted via the lymphatics from the tumor to the lymph nodes.¹¹⁻¹⁴ With the recent interest in immune scores in the tumor microenvironment the immune response in the sentinel node may provide valuable clinical information regarding the host response to breast cancer.

Indications for SLN Biopsy

Sentinel lymph node biopsy is indicated for staging patients with early T1-2 invasive breast cancer and clinically negative axillary nodes irrespective of surgical therapy on the breast.¹⁵ Women with DCIS undergoing mastectomy are SLNB candidates given the disruption of lymph channels during a mastectomy preventing accurate subsequent sentinel lymph node biopsies if invasion is identified.¹⁵ Other indications may include a patient with DCIS in whom large resection or oncoplastic procedure is required and may disrupt lymphatics a SLNB may be considered in that situation. SLNB can be considered in patients with ipsilateral recurrent breast cancer following breast conservative therapy or recurrence after mastectomy, while there have been case reports documenting successful SLNB after modified radical mastectomy or axillary dissection, this remains the exception rather than the norm.¹⁶

Contraindications for SLNB

Two absolute contraindications for a SLNB include patients with inflammatory breast disease and patients with clinically positive axillary nodes.¹⁷ These patients would require axillary lymph node dissection. Relative contraindications include ultrasound guided fine needle aspiration of an axillary lymph node proving metastasis. While surgeons traditionally have performed ALND in this patient population, others may choose to assess the patient for potential SLNB especially in the setting of neoadjuvant chemotherapy.^{15, 18} Use of lymphazurin blue due to possible teratogenic effects should be avoided during pregnancy for SLNB however radiotracers can be utilized alone instead.

Mapping Agents

Prior to surgery, the injection of dye and radioactive label is performed. In general, the combination of dye and radioactive label provides for the greatest identification of the sentinel lymph node.¹⁹ Sentinel lymph node identification rates have approached 96-100%^{19, 20} when both markers were used versus less than 86-90%^{20, 21} when single

agents were used. Additionally, the accurate identification of the sentinel lymph node using both markers have facilitated for smaller incisions.^{19, 21}

Options for dye include lymphazurin blue, or isosulfan blue, methylene blue, indocyanine green and indocarmine. The major radioactive label used is technetium 99. The anatomic placement of either dye or the radioactive label varies in the literature with intradermal versus subdermal placement of markers being described.^{22, 23} Additionally, markers have been subjectively placed in different regions of the breast with subareolar, peritumoral and intratumoral being described.^{22, 24} However, it is still unclear in which technique is superior with no existing large sample head to head study.²⁵ In general it appears that SLNB is successful independent of the site of injection. One place that is ineffective is injection into a seroma cavity.

Pre-Operative Lymphangiography

The use of lymphangiography preoperatively to identify axillary and internal mammary lymph nodes is controversial. Advocates for this argue that lymphoscintigraphy allows accurate preoperative location of the node and minimizes dissection.²⁶ Additionally, lymphoscintigraphy is unique in its ability to portray the internal mammary drainage.²⁷ However, the value of this information is controversial and still not uniformly recognized.^{28, 29} Opponents of the technique counter that lymphoscintigraphy provides no advantage with respect to node localization and that in fact lymphoscintigraphy has a higher false negative rate than the gamma probe technique for axillary lymph nodes.³⁰

Safety of the SLNB

The safety of the sentinel lymph node biopsy was underscored by the NSABP B-32 trial which showed that overall survival (OS), disease free survival (DFS) and regional control (RC) were statistically equivalent between the sentinel lymph node arm when the node was negative for disease compared to the sentinel lymph node and standard axillary node dissection (ALND) arm.³¹ Additionally, this high powered study showed that there was no statistical difference in axillary recurrences between the SLNB and ALND arms. Additionally, Veronesi et al. published 10 year single institutional results comparing outcomes in patients SLNB only to ALND in patients with clinically negative nodes.⁴ In this study, the SLNB negative patients did not receive completion ALND and results showed no statistical difference in breast cancer related events or OS between either group. This continued the trend in breast surgery supporting the concept that “less surgery was better” in the modern day surgical management of breast cancer.

Morbidity and risk of SLNB was further studied by the ALMANAC trial that showed that SLNB has significantly less morbidity than an axillary lymph node dissection. Specifically, patients who underwent SLNB only had statistically significant less lymphedema (RR=0.37), less extremity sensory loss (RR=0.37) shorter time to resumption of normal daily activities as well as improved patient-recorded quality of life and arm functioning scores.³² In sum, the SLNB is a safe operation with decreased morbidity compared to the axillary lymph node dissection in the node negative breast cancer patient.

Omission of ALND in the SLNB Positive Patient

The B32 trial demonstrated that SLNB was equivalent to ALND in terms of providing a satisfactory status of disease spread to the axilla. But this trial only showed that if the nodes were negative, that SLNB alone was sufficient to stage the axilla. The ACOSOG Z0011 trial sought to determine that if there were metastasis to the SLNs would SLNB alone be equivalent to ALND in terms of survival.³³ In women with T1-2 invasive breast cancer without clinically palpable nodes and one to two SLNs containing metastases the use of SLNB alone did not result in inferior survival than ALND. Of note, all women were treated with lumpectomy and whole-breast RT without axillary nodal radiation. The study sample did not address patients undergoing mastectomy nor did it address patients with three or greater positive lymph nodes.

Criticisms exist regarding these results. First, median average follow-up to this trial was 6.3 years although a counter to this criticism is that most recurrences occur before this time period. A second criticism was that the trial may have been underpowered due to early closure with a propensity for a Type II error. The goal was to accrue 1900 patients, but only 891 were entered into the trial. However, trends for lower locoregional recurrence and mortality favored the sentinel lymph node dissection only arm and were higher in the axillary dissection arm. Third, as all patients received whole breast radiation, there was a possibility that the radiation fields also affected the axilla and may have obliterated any nodal disease that was present thus resulting in decreased tumor cells in the remaining nodes and thereby creating a confounder. Lastly, some criticize that the number of events in the Z011 study, which determines the study's statistical power, was only 94 which was less than 20% of the planned number. Therefore, the study's applicability would be for low risk patients.

Two years after the results from Z0011 were published, the International Breast Cancer Study Group trial 23-01 (IBCSG 23-01) randomized patients with SLN micrometastasis (< 2 mm) and T1-2 invasive breast cancer to either completion ALND or no additional axillary surgery.³⁴ The primary end-points included five-year disease-free survival (DFS) and overall survival (OS) rates. Adjuvant radiation therapy was administered in 89% of patients undergoing an ALND and 92% of patients undergoing a SLNB only. There was no statistically significant difference in OS rate for patients treated with an ALND compared with those treated with a SLNB. The results of this trial, when considered in the context of the ACOSOG Z0011 trial, offers additional support to the concept that a subset of patients with metastases to sentinel nodes may in fact do well with SLNB alone compared to those who undergo completion ALND. Most Breast and Surgical Societies have issued consensus statements “that within a defined patient population (T1-2 invasive breast cancer with 1-2 positive SLNs treated with lumpectomy and whole breast radiation), one may consider no further axillary surgery.”

Neoadjuvant chemotherapy and SLNB

Neoadjuvant chemotherapy (NC) is offered to women with large primary breast tumors in order to shrink the primary tumor prior to definitive locoregional therapy. The optimal timing for SLNB in patients receiving NC has been debated, as some have reported a higher

false negative rate for SLNB performed after induction therapy³⁵ while others have not.³⁶⁻³⁸ The SENTINA trial noted a high false negative rate with SLNB performed after neoadjuvant chemotherapy.³⁵

Notable results of this study were that of the 592 women who converted from clinical node-positive to node-negative status, the SLN detection rate was 80 percent. When compared to completion axillary lymph node dissection, the false negative rate for SLNB was 14.2 percent. Notably, the fewer number of nodes harvested in a SLNB, the higher the false negative rate. When one or two nodes were harvested in the SLNB, the false negative rate was approximately 20%. A criticism of this trial to this point is that there is no long-term follow-up with regards to disease free survival, recurrence and mortality data. Similar to the SENTINA study, the ACOSOG Z1071 (Alliance) trial sought to determine the false negative rate (FNR) of SLNB after neoadjuvant chemotherapy for those patients with clinically-positive nodes that converted to clinically-negative node status. Similar to the SENTINA study, the ALLIANCE study confirmed that the FNR seemed to decrease when more than a single SLN was examined; 31.5% with one, 21% with two, and 9.1% with three or more.³⁹ Again, mortality, disease recurrence and disease free survival have not been reported and will be important in recommendations regarding SLNB timing with regards to neoadjuvant chemotherapy. Lastly, an oncologist has the option of obtaining an axillary ultrasound in the clinically negative axilla to better delineate the need for a SLNB versus an ALND.⁴⁰ The 2011 NCCN guidelines recommend that SLNB be performed prior to NC because it provides valuable prognostic information for planning locoregional treatment.

Sentinel Lymph Node Biopsy in the older patient

Given its minimally invasive, highly sensitive and reproducible record, SLNB has been shown to be a safe and accurate operation in the investigation of breast cancer nodal disease including those patients who were 70 and older.⁴¹⁻⁴⁴ The SLNB could negate the requirement for an ALND minimizing the risk of overtreatment in this age group. While the less invasive SLNB is viewed favorably in the older patient, there is still debate in whether or not the need for complementary ALND is necessary in the older age group. Javid et al. noted in the setting of a positive SLNB, that performing a completion ALND did not improve all-cause or breast-cancer-specific survival in women over 65 years of age.⁴⁵ In a retrospective review of the Surveillance, Epidemiology, and End Results (SEER) database, the five-year all-cause survival for patients with a positive sentinel node who underwent a completion ALND (n = 4586) did not statistically differ from similar women who did not undergo an ALND (n = 629), (84 v. 83 percent). In addition, there was no statistically significant five-year breast-cancer-specific survival (94.6 versus 91.6 percent). An analysis of prospective data is needed to confirm these retrospective findings.

Conclusion

The sentinel lymph node biopsy is a safe, reliable and reproducible operation that provides an accurate assessment of nodal metastasis for the breast cancer patient. It continues to add to the trend in breast surgery in which the surgeon provides less surgery while maintaining a standard of care that minimizes breast cancer morbidity and mortality.

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