

Sentinel lymph node biopsy in early-stage breast cancer patients: improved survival through better staging?

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Abstract

Purpose The objective of this review is to summarize the evidence demonstrating that the sentinel lymph node (SLN) procedure is not only associated with significantly less morbidity compared to the axillary dissection, but may also result in better staging and improved patient outcomes.

Methods A search of MedLine and PubMed articles using the terms “sentinel lymph node biopsy”, “breast cancer”, “staging”, “morbidity”, “survival”, and “outcomes” was conducted.

Results Breast cancer staging includes axillary evaluation as an integral component. Over the past two decades, sentinel lymph node biopsy has evolved as a technique that has an improved morbidity over traditional axillary dissection. The sentinel node(s) undergo a more intensive pathologic examination than traditional axillary contents. In the node-negative group of patients, this may have led to stage migration and potentially improved disease-free and overall survival.

Conclusion The SLN procedure is not only associated with significantly less morbidity compared to the axillary lymph node dissection, it may also result in more accurate staging, better axillary tumor control and improved survival.

Keywords Breast cancer · Sentinel lymph node biopsy · Outcomes · Staging

Introduction

Over one million women worldwide are diagnosed with breast cancer every year. Of those, over 300,000 will have disease that has metastasized to regional lymph nodes. Axillary lymph node status continues to be one of the most important prognostic indicators in breast cancer. As the surgical treatment of breast cancer has shifted from radical resections to less invasive approaches, the assessment of axillary lymph node status has followed suit [1].

The objective of this paper is to review the history of lymph node assessment, the development of sentinel lymph node biopsy (SLNB) and clinical outcomes after SLNB.

The history of axillary staging

Since the late 1990s, SLNB has become the standard method for staging the axilla in early stage breast cancer to determine axillary node status. The sentinel lymph node is the first lymph node to drain the organ in question. Many studies have demonstrated the accuracy of SLNB in predicting lymph node status [2]. SLNB has also been shown to have a low false negative rate, reported from 0 to 1.4 % [3, 4]. In 2005, Carlo et al. reported the results of a prospective trial examining the long-term outcomes of SLNB. This

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validation trial established the SLNB technique to be both accurate and to have a low false negative rate [4].

Morbidity after SLNB versus ALND

Axillary node evaluation is widely acknowledged to be the most important prognostic indicator in breast cancer [5]. Over the last 20 years, management of the axilla in early stage breast cancer has shifted away from formal axillary dissection towards minimally invasive sentinel lymph node biopsy. Traditional axillary staging is performed by levels I and II axillary lymph node dissection (ALND), where 10 or more lymph nodes are removed in a formal anatomic operation. However, complications from this surgery include pain, decreased shoulder range of motion, paresthesias, and chronic lymphedema, the latter being often the most debilitating for women after ALND. SLNB has shown to be associated with less morbidity, including decreased rates of lymphedema, sensory nerve damage, seroma formation, and hemorrhage compared to traditional axillary node dissection. Lucci et al. [6] reported the results of ACOSOG Z0011 comparing SLNB plus ALND to SLNB alone in node-positive patients. They reported adverse surgical effects in 70 % of the SLNB plus ALND group and 25 % in the SLNB only group. Patients in the SLNB plus ALND group had significantly more wound infections, seromas, and paresthesias. Although subjective reports of lymphedema were significantly different between the groups (13 % in the SLNB plus ALND group versus 2 % in the SLNB group), the difference in lymphedema almost reached statistical significance [6]. Langer et al. prospectively evaluated morbidity of SLNB versus SLNB plus ALND in 659 early stage breast cancer patients. Follow-up data was collected at approximately 30 months to evaluate presence of lymphedema, impaired shoulder range of motion, shoulder/arm pain, and numbness. In all cases, the SLNB group had significantly lower morbidity compared to the SLNB plus ALND group [7].

SLNB as a more accurate staging procedure

Pathologic examination of the sentinel node differs from the examination of conventional axillary contents. After ALND, axillary nodes are bivalved and stained with haematoxylin and eosin stain (H&E). One section from each half is then assessed. By comparison, the sentinel node is serially sectioned in 2–3 mm slices and undergoes both H&E and immunohistochemistry staining [8]. This much more thorough analysis is feasible due to the fewer number of nodes retrieved in SLNB as compared to ALND. The intensified pathologic approach has led to stage migration, and in

particular, upstaging when a node is positive by immunohistochemistry [9]. Most studies quote a 10 % upstaging of patients due to the more accurate pathologic examination of the sentinel node [1, 8, 9]. This upstaging may have a therapeutic impact, e.g., patients may receive adjuvant therapies, which they would otherwise not have been offered.

In 2008, Tan et al. published their results comparing methods of detection for SLNB versus conventional ALND. They examined axillary tissue from 368 node-negative breast cancer patients. These patients had been treated from 1976 to 1978 by mastectomy and axillary dissection. The axillary contents were initially examined by single sectioning and H&E staining. The paraffin blocks from the lymph nodes were re-examined using the current SLNB pathology protocol at Memorial Sloan–Kettering Cancer, which includes sections of 5–50 μm apart and stained both with H&E and immunohistochemistry [10]. A mean of 17 nodes per patient were assessed and 23 % of patients were reassessed as node-positive. Among these newly node-positive patients, 40 % were detected by H&E while 60 % were detected by immunohistochemistry. On univariate and multivariate analysis, the pattern of staining, number of positive nodes, number of metastatic cells, and cluster size were statistically significantly related to overall survival and disease-free survival. The authors concluded that in node-negative breast cancer patients staged by traditional pathologic examination, occult metastasis detected by SLNB pathology protocol is prognostically significant [10].

A review by Dowlatshahi et al. [11] evaluated 25 studies in which patients were deemed node-negative with standard histopathology. After re-evaluation, 24 of these studies identified lymph node metastases in 7–33 % of these originally node-negative patients. Most of the studies found significantly worse disease-free and/or overall survival. Indeed, many other studies have suggested [12–14] that node-negative patients who go on to develop local recurrence or distant metastases (up to 35–30 % at 10 years) do so as a result of missed nodal disease based on initial pathological assessment.

Does SLNB impact patient survival?

Node-positive patients

Bilimoria et al. [15] reviewed survival in sentinel lymph node-positive patients. In this study, 97,314 patients underwent SLNB and had nodal metastases. Of these patients, 20.8 % had SLNB only, while 79.2 % underwent completion ALND. Macroscopic nodal metastases (>2 mm) were evaluated separately from microscopic metastases (>0.2 to \leq 2 mm). In the macroscopic group, there was a nonsignificant trend to worse outcome (measured by axillary recurrence and overall

survival) in the SLNB-alone group versus the ALND group. However, in the microscopic group, there was no difference in either axillary recurrence or overall survival. From this, the authors concluded that while ALND does not appear to improve outcome in patients with microscopic nodal metastases, there is a trend toward better outcomes in those patients undergoing completion ALND with macroscopic nodal metastases [15].

The issue of survival benefit of ALND in sentinel node-positive patients has not been definitely settled. ACOSOG Z011 was the only prospective, randomized, multicenter trial comparing overall survival between sentinel node-positive patients that did and did not undergo ALND [16]. Despite the potential of being underpowered, recently published results of this study did not provide evidence that ALND in breast cancer patients with a positive SLN is associated with better overall survival. This randomized trial in fact suggested that the use of SLNB alone compared with ALND did not result in inferior survival in those patients treated with breast conservation and systemic therapy.

Node-negative patients

In the sentinel node-negative patient population, debate has centered on whether the more intensive pathologic examination of the sentinel node may be associated with improved survival. Traditionally this was thought to be part of the “Will Rogers Phenomenon”, i.e., stage migration and improvement in stage specific survival without a change in individual outcomes [17]. However, the presumed improvement may also be attributed to the additional adjuvant treatment offered to the upstaged patients. Vanderveen et al. reviewed data from their breast cancer registry of 893 patients over two different time periods, before and after implementation of SLNB. Their analysis showed a 5 % increase in single-node positivity in the SLNB group. Survival improvements were only seen in stage II patients in the SLNB group and this improvement in survival was attributed to stage migration [18].

A recent study by Montagna et al. focused on the impact of minimal lymph node metastases (i.e., micrometastases and isolated tumor cells) identification on survival [19]. Of the patients, 3,158 were designated as pN0 or pN1mi and were followed for a median of 6.3 years. Disease-free survival was noted to be worse for those patients with micrometastatic disease compared to node-negative patients if they underwent ALND [$n=1,071$] but not for those patients that underwent SLNB [$n=2,087$]. The authors concluded that lymph node micrometastasis identification is an important prognostic factor for those patients staged with ALND but not for those who underwent SLNB. The reason behind this is that in ALND, the size and/or number of metastases may be underestimated due to the less accurate scrutiny of the lymph nodes.

These retrospective studies support an important role of more accurate pathologic examination of SLNB compared to ALND regarding patient outcomes. This may result in stage migration, and hence patients may receive different or additional adjuvant therapies. Our group was the first to report prospective results in 2008. The objective of this investigation was to determine whether node-negative breast cancer patients undergoing SLNB have an improved DFS and OS compared to those undergoing ALND [20]. We compared 178 ALND patients (from 1990 to 1997) to 177 SLNB patients (from 1998 to 2004). The groups were from two distinct time periods reflecting the change in practice over the past 20 years [20]. In the SLNB group, a median of two lymph nodes was retrieved. All sentinel lymph nodes underwent intraoperative frozen section analysis with H&E at cut intervals of 150 μm . Nodes larger than 5 mm were bisected; those less than 5 mm were submitted completely for frozen section analysis. The residual tissue was formalin fixed and paraffin embedded. Permanent histologic analysis included both H&E and immunohistochemistry. In the ALND group, a median of 17 lymph nodes was removed. Nodes larger than 5 mm were bisected and one section from each half examined. Nodes 5 mm or less were not cut. H&E alone and no immunohistochemistry was applied to the ALND group [20]. Median follow-up was 49 months for the SLN group and 133 months for the ALND group. There were no differences in patient and tumor characteristics with the exception of tumor grade where the SLNB group had statistically significantly more grade I tumors and follow-up where the ALND group was followed longer [20]. Five-year overall survival and 5-year disease-free survival was significantly better in the SLNB group. After adjusting for confounding variables, the SLNB as compared to ALND was an independent predictor for both OS and DFS. Based on these findings, we concluded that the survival benefit is likely due to improved detection of tumor in the SLNB because of the more intensive pathologic scrutiny that the sentinel node (s) undergoes in comparison to the conventional treatment of the axillary node [20].

The MIRROR trial has found that adjuvant therapy in patients with SLN micrometastases is associated with improved disease-free survival [21]. However, the study did not address the appropriate surgical management of the axilla in this situation. In our prospective trial, patients with SLN micrometastases without ALND were followed for a median of 77 months. There was no significant difference in either axillary recurrence or survival between those patients that underwent completion ALND and those that did not [22–25].

Conclusion

Axillary evaluation continues to be an integral component of breast cancer staging. SLNB is a procedure that has

shown an improved morbidity over traditional ALND as well as an acceptable false negative rate. In node-negative patients, the more intensive pathologic examination of the sentinel node(s) may lead to a stage migration and potentially improved disease-free and overall survival. The upstaged patients may receive additional, potentially beneficial therapies, which they would not have been offered after ALND. The SLN procedure is not only associated with significantly less morbidity compared to the ALND, it may also result in more accurate staging, better axillary tumor control, and improved survival.

Conflicts of interests None

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