Sentinel Lymph Node Biopsy in Early Breast Cancer: the First 100 Cases Performed in a Teaching Institute

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Abstract

Background: The histologic status of axillary lymph nodes is one of the most important prognostic factors in breast cancer and influences the management of these patients. Axillary lymph node dissection was traditionally performed in all patients to obtain this information but this procedure carries a considerable rate of complications. Recently, sentinel lymph node biopsy has emerged as an accurate and minimally invasive tool for predicting the axillary nodal status and has become the standard of care in selected patients with breast cancer.

Objective: To examine the accuracy of SLN biopsies performed by surgical residents during surgical resident training.

Methods: This prospective, randomized controlled study included 100 consecutive patients with clinically early breast cancer (T1-T2, N0, M0). Lymphatic mapping was performed using radiotracers, blue dye, or both. Formal axillary lymph node dissection completed the operations in all patients. All operations were performed by surgical residents under the supervision of senior surgeons.

Results: The overall rate of identification of sentinel lymph nodes was 92%. The accuracy of SLN biopsy in reflecting the axillary nodal status was 96% with a false negative rate of 5.7%.

Conclusions: Sentinel lymph node biopsy is an accurate method for the evaluation and staging of regional lymph nodes in breast cancer patients. A dedicated instruction program for surgical residents may increase the standard of care and lead to highly trained surgeons in the management of early breast cancer.

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Staging of patients with invasive breast cancer and clinically negative regional lymph nodes remains the primary goal of axillary lymph node dissection [1,2]. The histologic status of these nodes is still one of the most important prognostic factors in patients with breast cancer and directly affects the clinical management. Detection of regionally involved lymph nodes predicts a 40% reduction in the 5 year survival rate [3]. However, in as many as 60% of patients with palpable early breast cancer and in 90% of patients with occult invasive breast lesions the resected nodes are clear [4,5]. Nevertheless, over 80% of women who undergo axillary lymph node dissection have at least one postoperative complication, including infections, hematomas, decreased sensation and reduced movement range of the arm [6–8]. The high rates of complications and negative resections on one hand, and the important value of the histologic status of the regional nodes on the other, encouraged the development of a potentially alternative method to formal ALND, namely, sentinel lymph node biopsy. The sentinel lymph node was defined by Cabanas in 1976 [9] as the first node to receive lymphatic drainage from a solid tumor and should, theoretically, have the earliest detectable lymphatic tumor. In 1992 Morton et al. [10] used blue dye to identify the lymphatic duct that drained into the sentinel lymph nodes of patients with malignant melanoma. The localization of the sentinel node in breast cancer by radiotracers was reported by Krag and associates [11], and not long after, Giuliano et al. [12] were the first to report the successful use of blue dye in breast cancer. Albertini [13] examined the yield of combining the two methods, suggesting the synergistic effect of this combination.

The primary goal of sentinel node evaluation is to accurately stage patients using a less morbid procedure. There is also evidence to suggest that by studying a smaller number of lymph nodes with greater scrutiny using immunohistochemical stains and deeper sections, micrometastasis can be detected [14]. Overall, as experience in this field grew, the reported accuracy of SLN biopsy with respect to the regional lymph node status was high (97%) [15] and additional controlled studies are now in progress. Furthermore, in institutions with established high SLN biopsy performances, selected patients are enrolled to SLN biopsy without formal ALND if the former is free of tumor deposits [16].

In the present study we report our initial experience in sentinel lymph node biopsy in patients with early breast cancer performed by surgical residents.

Patients and Methods

Patients

Between December 1998 and December 2001 we studied 100 consecutive patients with early invasive breast cancer (clinical stages T1-T2, N0, M0). Excluded from this study were patients with clinical evidence of axillary metastasis, previous axillary lymphadenectomy, locally advanced disease, ductal carcinoma *in situ*, or pregnant or lactating women. Ages of the women enrolled in this study ranged from 41 to 83 years, mean 51 years. Seventy-one patients had tumors $\leqslant$ 2 cm (T1) and 29 patients had tumors of 2–4 cm (T2). Preoperative histologic diagnosis was confirmed by open

SLN = sentinel lymph node

ALND = axillary lymph node dissection

biopsy of a palpable lesion in 47 patients and by open biopsy with needle localization in 12 patients. In 41 patients malignancy was detected by cytologic analysis obtained by fine-needle aspiration. Invasive ductal carcinoma was the commonest pathology encountered and was found in 82 patients. Less common malignancies were found in 18 patients: invasive lobular carcinoma in 8, invasive tubular carcinoma in 4, combined invasive tubuloductal carcinoma in 4, and invasive mucinous carcinoma in 2. The operations were performed by five surgical residents at different stages of their residency (the youngest of them being in her second year of residence), under the supervision of senior attending surgeons. In 82 patients conservative breast surgery with lymphadenectomy was performed and another 18 patients underwent modified radical mastectomy.

Lymphoscintigraphy

Lymphoscintigraphy was performed after peritumoral injection of radiolabeled colloid, which was drained and then phagocytized by the regional lymph nodes [17]. We used 400 μcurie Rhenium colloid labeled with Technetium-99m, which was injected 4–24 hours before surgery to the breast tissue surrounding the primary tumor. At the time that the study was initiated we usually injected the isotope 16–24 hours before the operation, based on recommendations in the literature [17]. Following additional studies showing that the isotope can be injected on the day of the operation with a similar success rate [11], we began to inject the isotope only 4 hours before surgery. Scintigraphic images were obtained 5, 10, 20, 60 and 120 minutes after injection using a large-field-of-view gamma camera equipped with a parallel hole, low energy and high resolution collimator. Planar anterior and oblique lateral scans of the breast and axillary region were obtained to determine the exact position of the sentinel node. Delineation of body contour was obtained using flood source of ^{57}Co (Amersham, UK). A body contour was obtained with a Co57 phantum.

Operative technique and pathologic analysis

We injected 2 ml isosulfan blue dye (Patent Blue Sodium Guerbet 2.5%, Guerbet, France) intradermally into the breast surrounding the tumor (or biopsy site) in the operating room 5–10 minutes before surgery. A hand-held gamma counter was then used to localize the radioactive SLN. We first defined the perimeter of the radioactive tracer diffusion zone around the injection site, and then examined the axilla, the breast and the surrounding tissue for discrete regions of radioactivity. The site of the incision was selected with the aid of the hand-held gamma counter. All the radioactive nodes encountered were removed until the background radiation in the axillary bed disappeared. Radioactivity of the resected nodes was always determined away from the operative field. Similarly, all stained lymph nodes were removed. Blue dye localization was considered successful if a stained lymph node was identified during exploration of the axillary region. Isotope localization of a sentinel lymph node was defined as an area of localized radioactivity separate from the injection site with at least 25 counts per 10 seconds. Dye-only or isotope-only success rates (the marginal benefit) were defined as the proportion of cases in which the SLN was identified by only one of the methods. The overall identification rate (the total success rate) was defined as the percentage of SLN identified by either of the methods, alone or in combination.

A formal lymphadenectomy including levels I and II was then performed in all patients. Pathologic examination included review of paraffin sections stained by hematoxylin and eosin from lymph nodes found in the specimen. Lymph nodes from the axillary dissections were sectioned two or three times. Sentinel lymph nodes were processed by at least six serial sections, stained with hematoxylin and eosin, and one section (usually level III) was stained for anti-cytokeratin by a cocktail of low and high molecular weight monoclonal antibodies.

Statistical analysis

One-way analysis of variance and chi-square tests were used for statistical analysis. A P value of <0.05 was considered significant.

Results

Sentinel lymph nodes were identified in 92% of the patients enrolled in the study (92 of 100). When radiolabeled isotopes were used, sentinel nodes were detected by a hand probe in 81.3% of the patients (74 of 91). When blue dye was used the detection rate was 72% (67 of 93), which was significantly lower than the rates observed for the radiolabeled method ($P < 0.05$). In 61 of 88 patients (69.3%), sentinel lymph nodes were identified by both blue dye and gamma probe. The mean number of sentinel lymph nodes and non-sentinel axillary lymph nodes removed from each patient was 1.8 (range 1–3) and 15 (range 8–35), respectively. Among the 92 patients in whom one or more sentinel lymph nodes were identified, sentinel nodes were limited to one location in 85 patients (92%), to two locations in 6 patients (6.5%), and to three locations in one patient (1%).

Table 1 illustrates the definitive pathologic results for the 92 patients in whom a SLN was identified. The sentinel node was found to be metastatic in 39 of 92 patients (42.3%): in 22 of 39 (56.4%) the sentinel node was the only metastatic axillary node, while in 17 of 39 (43.6%) other metastatic axillary nodes were also found. In four patients micrometastases were only detected by immunohistochemistry for anti-cytokeratin and were not observed by standard hematoxylin and eosin staining. In 53 of 92 patients (57.6%) the sentinel node did not harbor metastasis. In 50 of these patients (94.3%) no other axillary node showed metastatic involvement, while in 3 cases metastasis was discovered in non-sentinel nodes, resulting in a false negative rate of 5.7%.

Table 1. Concordance between sentinel node and other axillary lymph nodes at the definitive histologic examination

Sentinel nodes	Other axillary nodes	No. of patients
Positive	Positive	17
Positive	Negative	22
Negative	Negative	50
Negative	Positive	3

The observed sensitivity of finding a histologically positive sentinel node was 85% (17 of 20). The specificity by definition was 100%. The overall accuracy of sentinel nodes in assessing the presence of metastatic disease was 96.7% (89 of 92). The positive predictive value was 43.5% (17 of 39), and the negative predictive value 94.3% (50 of 53).

Discussion

Sentinel lymph node biopsy has become the standard of care in the evaluation of axillary nodal involvement and is used routinely worldwide. We began to perform SLN biopsies some 4 years ago as part of the resident training program in a teaching hospital. Our results show high accuracy rates in determining the correct nodal status, similar to the rates published in previous studies [17]. With meticulous and dedicated training, a high performance rate can be achieved by surgical residents, preparing them to provide the standard of care in breast cancer as independent surgeons in the future.

Although SLN biopsy has been shown by numerous studies to be highly accurate, errors do occur. In our study we encountered three false negative cases in which the SLN was tumor-free but metastasis was detected in other non-sentinel nodes. We examined these cases in order to understand what led to this failure but unfortunately could not find a feasible explanation. Some authors have speculated that the skin area where the radiolabeled isotope was injected had a lymphatic drainage different to that of the tumor, or that rarely were there true skip metastases [17]. One study found that all the false negative results occurred when the primary tumor was in the lateral half of the breast [15]. Other studies concluded that the rate of false negative biopsies was increased in operations performed in patients with previous excisional biopsies [18]. However, none of these findings was applicable to the present study. The location, methods of histologic/cytologic diagnosis and time of injection were different in each of these cases. In two of the false negatives, SLNs were detected by radiotracers alone and one was detected by both blue dye and radiotracer.

Several methods are employed for lymphatic mapping in breast cancer, including blue dye, radiotracers, or a combined approach using both blue dye and radiotracers. Nevertheless, there is no consensus as to which is the optimal technique. Individual experts have reported excellent results with the use of single-agent SLN mapping, but these results are not representative of those reported by all investigators. Most notably, reports from Giuliano and colleagues [19] and Kern [20] demonstrated high success rates of 93% and 98%, respectively, with the use of blue dye alone without any false negative results, but the collective published literature for blue dye mapping reports a mean success rate of only 81% and a false negative rate of 9% [21]. Veronesi and co-workers [22] reported a 99% success rate with isotope alone and 7% false negative results, similar to subsequent studies. In our department we use the combined technique of blue dye and radioisotope mapping as advocated by Albertini [13]. Our results show that while the identification rate for blue dye and radiotracers was 71% and 82% respectively, the overall identification rate was 92%, suggesting that the use of the combined technique results in a higher success rate.

The optimal injection site for radioactive colloid injection technique for breast SLN biopsy has not been defined. Veronesi et al. [22] found that subdermal injection of radioactive colloid resulted in an SLN identification rate of 98.2% and a false negative rate of 4.7%. Kelly et al [23], comparing the SLN identification rates obtained from different injection sites, reported rates of 89.9%, 95.3%, and 98.0% when the radiotracer was injected to the peritumoral, subdermal, and intradermal areas, respectively. Although the highest rates in that study were achieved by intradermal injection, it did not decrease the rate of false negative findings.

The technique of SLN biopsy requires significant training, and axillary lymph node dissection should not be abandoned until the entire team is able to achieve highly accurate results. In the present study all patients enrolled to SLN were also subjected to ALND to evaluate the ability of SLN biopsy to accurately reflect the nodal status. Theoretically, if ALND had been reserved in this study for patients with positive sentinel nodes only, 50 patients would have been spared the cost and morbidity of axillary dissection, at the price of 3 cases of undetected axillary metastases. Indeed, the data overwhelmingly permit the simple conclusion that a tumor-free sentinel node is indicative of node-negative breast cancer in at least 95% of cases in experienced hands [24]. We therefore apply this concept in our department as part of the high standard of care of eligible breast cancer patients. Finally, our results suggest that dedicated teaching of the sentinel lymph node biopsy technique by senior surgeons may lead to a high level of competency when these biopsies are performed by surgical residents.

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