Survival analysis following sentinel lymph node biopsy: a validation trial demonstrating its accuracy in staging early breast cancer

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Few long-term follow-up studies prove sentinel lymph node biopsy (SLNB) effectively stages breast cancer without the further evaluation of a completion axillary dissection. Our prospective study addressed this issue, enrolling 345 women with clinically node-negative breast cancer who underwent SLNB from October 1997 through December 2000. The median age of the patients in the study was 56.7 years. Average primary tumor size was 1.42 cm. Ninety-three patients had a positive sentinel lymph node (27%); 70 (75.3%) of these patients underwent completion axillary dissection, while 23 patients (24.7%) declined further surgery. Most (91.3%) of the patients who declined further surgery had evidence of micrometastatic disease only. The median follow-up period for all patients was 60 months. No tumor recurrences in the axilla were reported in either sentinel node-negative or -positive patients. The local and systemic recurrence rates were 3.1% and 4% in node-negative patients and 2.2% and 4.3% in node-positive patients. Two patients (0.9%) in the node-negative group and 6 (6.5%) in the node-positive group died of their disease. Estimated 5-year disease-free survival rates were 96% for node-negative patients and 87% for node-positive patients ($P = 0.02$). The clinical false-negative rate of the SLNB in this study was 0%. This long-term validation trial proves the accuracy of the SLNB and its extremely low false-negative rate. The findings indicate that patients with a positive SLNB have significantly different survival rates than patients with a negative SLNB.

Breast cancer is currently the leading type of cancer among US women and the second leading cause of cancer death. With the risk reported to be 1 in 9 or even 8 (1), it is more important than ever to provide not only effective screening methods but also accurate ways to determine prognosis once the diagnosis has been established. Accurate stage, including axillary lymph node status, continues to be one of the most important prognostic indicators of outcome in women with breast cancer (2–5). Standard management of the axilla in breast cancer is a complete axillary dissection (AD), which provides both treatment and information on nodal status (5–8). However, the acute complication rates for the procedure are reported to be 20% to 55%, and these complications include lymphedema, sensory nerve damage, hemorrhage, and seroma formation (9–11). Additionally, chronic arm lymphedema rates of 7% to 56% are reported (12–14).

The pioneering reports of Krag et al (15) and Giuliano et al (16) allowed the sentinel lymph node biopsy (SLNB) to serve as a stand-alone method for determining axillary nodal status. The sentinel lymph node (SLN) is the first lymph node to drain the entire lymphatics of the breast. Since metastatic breast cancer cells travel via this route, an SLN free of metastatic cancer, in theory, indicates that the remainder of the nodal basin is also negative for metastasis (17). Many studies have shown that SLNB accurately predicts axillary lymph node status (18–20), and SLNB has been shown to be associated with less morbidity than a completion AD (9, 21). Additionally, SLNB has a low clinical false-negative rate of 0% to 1.4% (20, 22–26). As a result, many medical centers are now using SLNB without a completion AD in patients who have a negative SLN (27). However, only one randomized prospective trial has demonstrated SLNB's accuracy as a screening method comparable to a completion AD (28). Moreover, the long-term outcome of SLNB without a completion AD has not been fully evaluated. The purpose of this study was to evaluate the early accuracy of SLNB at this institution and through patient follow-up to determine whether the information gathered correctly predicts the clinical course of disease progression.

METHODS

Patients

From December 1997 to October 2000, patients were enrolled in a single-institution prospective trial under the approval of the institutional review board. Criteria for enrollment included a histological diagnosis of invasive breast cancer, a primary tumor <5 cm, a clinically negative axilla, and informed consent. Patients were excluded from the study for a clinically positive axilla, pregnancy, previous axillary lymphadenectomy, multiple primary tumors, or tumors >5 cm.

Operative technique

The technique for SLNB at our institution during study enrollment included the use of blue dye and technetium Tc 99m sulfur colloid. The Tc 99m sulfur colloid was prepared by the nuclear medicine department and comprised an unfiltered solution containing a 1.0-mCi volume of solution diluted to a total volume of 8 mL using normal saline. The solution was then injected around (but not into) the tumor or biopsy cavity using 2-mL aliquots in the superior, inferior, medial, and lateral dimensions. The time interval from injection to surgery ranged from 30

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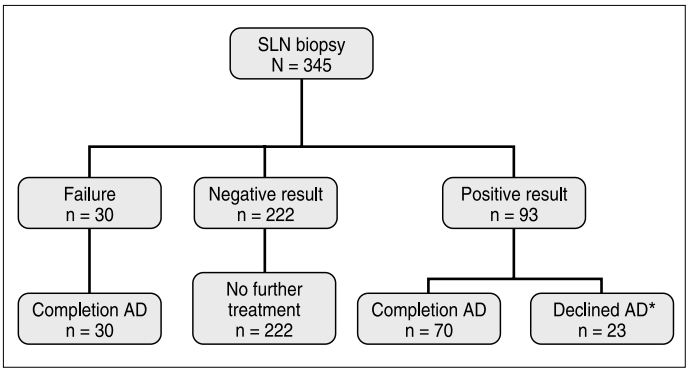

Figure 1. Schematic diagram of the SLN treatment algorithm and the creation of four treatment population groups. SLN indicates sentinel lymph node; AD, axillary dissection. *The surgeon recommended a completion AD, but the patient declined it.

minutes to 8 hours. During surgery, blue dye (1% isosulfan blue) was injected around the tumor or biopsy site in four deposits of 3 to 5 mL each.

Upon completion of the blue dye injection, the patient was prepped and draped in routine sterile fashion. A low transverse axillary incision was then made, and the clavipectoral fascia was incised. A gamma probe (C-Trak, Care Wise Medical Products, Morgan Hill, CA) was used to locate "hot" nodes. All "hot" nodes having a detected radioactivity >25 counts per 10 seconds were removed, as were any observed blue nodes. Once all nodes were removed, the axillary incision site was assessed. The procedure was deemed successful if the background radioactivity counts in the wound were <10% of the measured counts of the hottest excised lymph node.

Pathological examination

All excised lymph nodes were carefully labeled and evaluated by a pathologist. All blue and "hot" nodes were labeled as sentinel nodes. Any excised nodes not containing blue dye or having measured radioactivity counts <10% of that of the hottest node were labeled nonsentinel nodes. Nonsentinel lymph nodes and lymph nodes collected from AD were sectioned and examined grossly for tumor cells. SLNs were analyzed by frozen sectioning at the discretion of the surgeon or pathologist. Those not subjected to frozen sectioning were sectioned in 1-mm to 2-mm intervals and stained with a hematoxylin and eosin solution. If the specimens were negative for tumor cells, they were further analyzed by immunohistochemical staining. An SLN was negative for tumor cells if both the hematoxylin and eosin and immunohistochemistry results were negative. If either study demonstrated evidence of tumor cells, the surgeon recommended completion AD.

Follow-up and adjuvant therapy

Patients were monitored by their surgeon immediately after surgery, every 6 months for 5 years, and yearly thereafter. Each visit included a physical examination and detailed history. Diagnostic examinations such as mammograms or sonograms were obtained as indicated. All patients were referred to a breast oncologist and offered chemotherapy and/or antiestrogen therapy according to established guidelines at that time. Patients undergoing breast conservation therapy were given radiation treatments to the ipsilateral breast under the guidelines and protocols of a radiation oncologist. No direct axillary radiotherapy was given to any study patient.

Table 1. Disease characteristics

Characteristic	n (%)
Biopsy type	
Core	188 (54.5)
Core/excisional	4 (1.2)
Excisional	129 (37.4)
Fine-needle aspiration	23 (6.7)
TruCut	1 (0.3)
Primary tumor size	
T1mic	12 (3.5)
T1a	23 (6.7)
T1b	94 (27.2)
T1c	160 (46.4)
T2	56 (16.2)
Type of surgery	
Partial mastectomy	299 (86.7)
Partial mastectomy with reexcision of margins	18 (5.2)
Mastectomy	28 (8.1)
Histology	
Ductal	283 (82.0)
Lobular	21 (6.1)
Mixed ductal/lobular	26 (7.5)
Tubular	5 (1.4)
Mucinous	8 (2.3)
Colloid	1 (0.3)
Apocrine	1 (0.3)
Receptor status	
ER^+/PR^+	242 (70.1)
ER^+/PR^-	33 (9.6)
ER^-/PR^+	16 (4.6)
ER^-/PR^-	53 (15.4)
Adjuvant therapy	
Chemotherapy	172 (49.9)
Hormonal therapy	283 (82.0)

ER indicates estrogen receptor; PR, progesterone receptor.

Statistical analysis

Pertinent data, including patient demographics, tumor characteristics, and follow-up information, were recorded in a Microsoft Access database. All disease-free survival periods were censored at 5 years. Patients who died of other causes were censored at the time of death. A Kaplan-Meier approach was used to model the disease-free survival periods. Stratified analyses were performed by SLN status, initial stage, and number of positive axillary lymph nodes (29). A log-rank test was used to test for differences among the strata. A similar approach was used to compare the disease-free survival rates between SLN-positive patients and patients who declined AD. Other study endpoints included evidence of tumor recurrence in either the axilla or primary tumor site and development of metastatic disease.

Table 2. Disease status at end of follow-up period

Reported status	SLN-negative patients (n = 222)	SLN-positive patients refusing completion AD (n = 23)	SLN-positive patients with completion AD (n = 70)
Alive with disease (bone metastases)	4 (1.8%)	—	2 (2.9%)
Alive with disease (other metastases)	3 (1.3%)	1 (4.3%)	—
Died of disease	2 (0.9%)	2 (8.7%)	4 (5.7%)
Died of other causes	8 (3.6%)	—	2 (2.9%)
Local recurrence	7 (3.1%)	—	2 (2.9%)
New primary tumor	4 (1.8%)	—	1 (1.4%)
No evidence of disease	197 (87.5%)	20 (87.0%)	59 (84.3%)

RESULTS

A total of 345 patients were enrolled in the study *(Figure 1)*; their average age was 56.7 years (range, 29–85 years). *Table 1* shows the disease characteristics. Most patients underwent a partial mastectomy or lumpectomy followed by adjuvant radiotherapy under the supervision of a radiation oncologist. In most cases, the SLN procedure was completed concurrently with the partial mastectomy. The average primary tumor size in the study population was 1.42 cm (range, 0–4.05 cm). Most of the tumors had invasive ductal features. Adjuvant chemotherapy was administered to 172 patients (49.9%), and hormonal therapy was given to 283 patients (82%).

The overall success rate in acquiring an SLN either by radioactive tracer identification or blue dye observation was 91.3%. In 24 cases, the blue dye and radioactive isotope failed to migrate to the axilla. Technical failures, including intraoperative problems with the equipment, occurred in another 6 cases. All patients who had an intraoperative failure underwent completion AD at the time of surgery. The estimated 5-year survival rate for patients completing the SLNB protocol was 94% (95% CI, 91%–97%). The average number of SLNs acquired was 2.36.

Table 2 summarizes follow-up data for all patients. A total of 222 patients had a negative SLNB result. Nine patients (4%) in this group eventually developed evidence of metastatic disease, of whom 2 patients (0.9%) died of disease. Seven patients (3.1%) had a local recurrence (ipsilateral breast), and 4 (1.8%) developed a new primary tumor (contralateral breast). No incidences of axillary recurrence were reported during the follow-up period; thus, the clinical false-negative rate for this group was 0%. The estimated 5-year disease-free survival rate for patients with node-negative disease was 96%.

A completion AD was indicated for all patients with positive nodes, whether sentinel or nonsentinel. Of the 23 patients who declined to undergo this procedure, 21 (91.3%) had demonstrable evidence of only micrometastatic disease (<2 mm) on immunohistochemical staining. No patient with a positive SLN who did not undergo a completion AD in this study developed axillary disease. All patients who refused completion AD were given adjuvant therapy, which included chemotherapy and hormonal therapy. The disease-free survival rate of patients electing not to undergo a completion AD was not significantly different from that of patients with a positive SLN who did undergo a completion AD ($P = 0.47$).

Among the 70 patients who had a positive SLNB result and underwent completion AD, 25 (35.7%) had micrometastatic disease (<2 mm focus) and 45 (64.3%) had macrometastatic disease (≥2 mm) in the SLN. Fifty-three (75.7%) of the patients had only one positive SLN, and 17 (24.3%) had >1 positive SLN. In the 25 patients with micrometastatic disease in the SLNB, 4 (16%) had additional diseased lymph nodes upon completion AD. Among those with macrometastatic disease in the SLNB, 14 patients (31%) had additional diseased lymph nodes upon completion AD. Most patients with a positive SLN received adjuvant therapy: 93% received chemotherapy and 86% received hormonal therapy. As seen in *Figure 2*, the survival curve for patients with a positive SLN differed significantly ($P = 0.02$) from that of patients with a negative SLNB result, and the estimated 5-year survival rate was 89% for all patients with a positive SLN.

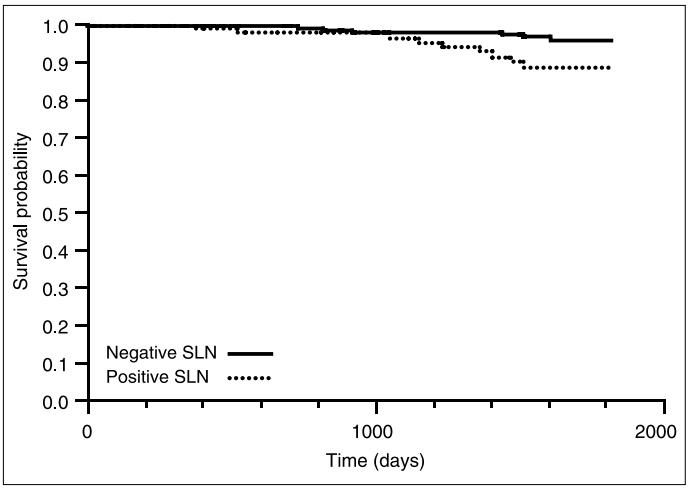

Figure 2. Survival curves for patients with negative and positive sentinel lymph node biopsy results.

In this study, 6 patients who had a negative SLNB result went on to undergo completion AD at the discretion of the surgeon. In 3 of these patients, the additional excised lymph nodes were all negative, but the other 3 patients had positive nonsentinel nodes despite a negative SLN. One patient with a negative SLN had tumor infiltrating a node in the lumpectomy specimen. Because of this, she underwent completion AD, which revealed 2 positive axillary lymph nodes. One of the other 2 patients had an additional positive lymph node on AD. All of these patients remained alive during the study period without evidence of further disease.

The SLNB results and primary tumor size were used to stage each patient's disease under the current staging guidelines of the American Joint Committee on Cancer. *Figure 3* shows the different survival curve groupings based on these data. A log-rank test comparing these curves demonstrates a difference ($P < 0.001$) in disease-free survival rates between the stage groupings, indicating that initial staging has a significant impact on disease severity.

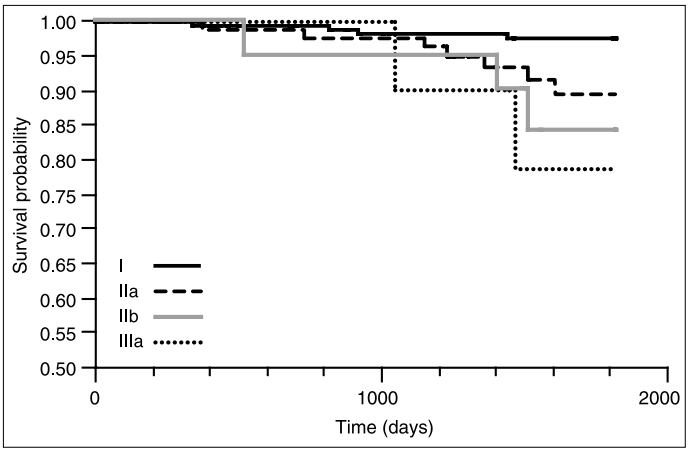

Figure 3. Survival curves grouped by stage.

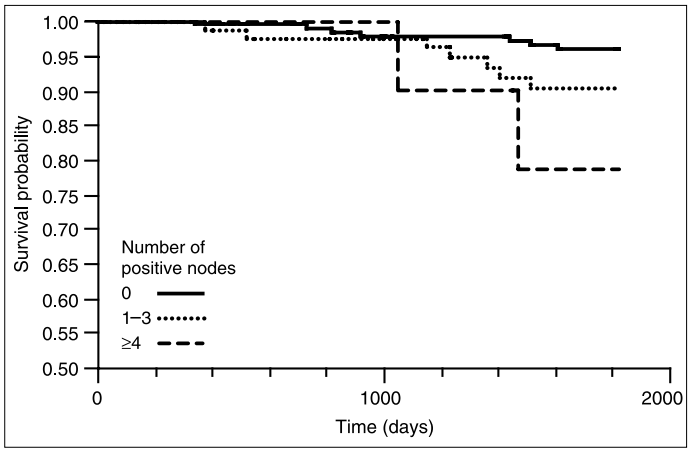

Figure 4. Survival curves grouped by number of positive axillary lymph nodes.

Figure 4 demonstrates survival curve differences in patient groupings based on the number of positive axillary nodes. Log-rank analysis again demonstrated a statistically significant difference ($P = 0.04$) between the survival curves. Furthermore, the number of positive nodes clearly affected disease severity, as evidenced by the progression of the survival curves.

DISCUSSION

The purpose of this study was to prospectively evaluate the accuracy of the SLNB in women with early stage breast cancer. The studied patient cohort represents the first patients undergoing this procedure by surgeons at this institution without a completion AD for validation. Each surgeon who participated in this study demonstrated his or her ability to execute the procedure by completing a trial of SLNB followed by a completion AD in 20 patients. Each surgeon needed to demonstrate an accuracy of 100% in his or her validation trial before being allowed to enroll patients in this study and thus perform SLNB at this institution.

Based on the experience of our surgeons as well as new techniques described in the literature, changes have been made in the way SLNB is performed at this institution. During the study period, there were 24 instances in which both the blue dye and the radioactive tracer failed to migrate into the axilla. In those cases, the surgeon was forced to perform a completion AD, and the SLNB was designated a "failure to migrate." This recognition rate of 91.3% has significantly improved at this institution, with surgeon experience and the use of deep dermal injections of dye/tracer rather than peritumoral injections used during the study period.

No patients with a negative SLNB result subsequently developed axillary disease during the study period. Other studies have reported similar favorable clinical false-negative rates, though the current study demonstrates a longer follow-up period than other published reports (8, 16, 20, 28). Having a very low false-negative rate is of paramount importance because prognosis and treatment strategies depend heavily on the true axillary nodal status. This study demonstrates that a negative SLNB result can accurately predict a clear axilla free of metastatic disease.

Patients who had a negative SLNB result were shown to have an excellent 5-year disease-free survival rate. This correlates well with known survival rates in patients with stage I disease. Given this information, a patient with a negative SLNB result can be accurately designated as having a favorable prognosis; however, this cannot be fully determined without taking into account other factors such as hormone receptor status, primary tumor size, and primary tumor characteristics. This study, unfortunately, is not significantly powered to determine whether a negative SLNB result correlates with a higher disease-free survival rate after adjusting for these other factors.

Patients with a positive SLNB result had a significantly lower 5-year disease-free survival rate than patients with a negative SLNB result. Again, this correlates well with established stage II and stage III survival information. Patients having evidence of micrometastatic (<2 mm) disease on the SLNB were grouped in this study as having positive biopsy results. Again, this study was not powered to detect the independent significance on survival or the probability of having additional positive LNs when comparing micrometastatic vs macrometastatic disease.

Of the 23 patients who had evidence of micrometastatic disease in their SLNB but elected not to undergo completion AD, none developed axillary recurrence during the study period. Twenty-two of these 23 patients received chemotherapy (95.8%), and 20 received hormonal therapy (87%). All 23 underwent local breast irradiation, and one might conclude that these adjuvant measures were protective for the axilla and helped to prevent axillary disease. However, data from additional clinical studies, such as the AGSOG Z-11 trial, are needed to determine whether a completion AD is necessary for micrometastatic disease.

Of the 3 patients who had a negative SLNB result but had positive nodes in or near the axilla, 2 had the adjacent nodes taken during the SLNB procedure because the surgeon thought the nodes appeared abnormal. This demonstrates an important part of the SLN procedure, which is to inspect the axilla and remove any nodes that appear abnormal. The third patient had a positive lymph node in the lumpectomy specimen. This indicated that the drainage basin of the lymphatics to the axilla may have been disrupted, and while the SLN was negative for tumor, a completion AD is prudent if there is any doubt about the integrity of the SLNB result.

The initial characteristics of each patient's disease, including primary tumor size and axillary lymph node status as dictated by the SLNB result, were used to place patients in staging categories. Follow-up information clearly showed the risk of disease

progression to be higher in patients with larger tumors and/or positive SLN. If the survival rates of the patients in this study are compared with known survival rates in the literature, the SLNB seems to be an accurate method of staging breast cancers and estimating survival rates.

The SLNB is currently the treatment standard for patients with early breast cancer at this institution. This prospective study further validates its usage because of its accuracy in detecting axillary lymph node metastasis and the lack of axillary recurrences through the follow-up period. Furthermore, the follow-up observations of patients in this study demonstrated that SLNB correctly staged their breast cancers as determined by the 5-year survival differences. In conclusion, the SLNB is a successful method of staging breast cancer and should be a part of the standard of care in this disease.

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