Sentinel Lymph Node Technique for Staging of Breast Cancer

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Key Words. Sentinel node · Axillary lymphadenectomy · Breast cancer · Lymphatic mapping

ABSTRACT

Lymphatic mapping and sentinel lymphadenectomy is becoming an important surgical technique for assessing axillary status in breast cancer. In experienced hands, it can be successfully performed in >90% of cases. The morbidity of sentinel lymphadenectomy is minimal, considerably less than the 15%-20% rate of complications associated with axillary lymph node dissection. Moreover, excision of the sentinel node provides a specimen for focused histopathologic analysis and experimental studies using sensitive immunohistochemical techniques and even reverse transcriptase polymerase chain reaction, which may improve detection of axillary metastases. Intraoperative mapping of the lymphatic tract draining to the sentinel node may use vital blue dye and/or radioactive tracer. The rate of sentinel node detection exceeds 90% with either agent alone or in combination. Because definitive follow-up data are not yet available, intraoperative lymphatic mapping and sentinel lymphadenectomy should be considered an experimental staging adjunct rather than a therapeutic modality. The Oncologist 1998;3:165-170

INTRODUCTION

Axillary lymph node status is the most important prognostic indicator for patients with primary breast cancer [1, 2]. The prognostic significance of axillary nodal involvement also extends to the number of nodes involved [3]. Axillary lymphadenectomy (ALND) with histopathologic study of the axillary specimen remains the gold standard for detecting axillary nodal involvement and determining the number of nodes involved [4]. However, the low (<3%) rate of axillary recurrence in patients undergoing level I-II ALND [5-7] is achieved at the cost of significant morbidity, with an acute complication rate of 20%-30% and a chronic lymphedema rate as high as 20%-30% [8-12]. Therefore, routine ALND is controversial in breast cancer patients who have a low risk of axillary metastasis or who would receive adjuvant therapy regardless of axillary involvement. At present, there are no adequate noninvasive techniques for assessment of axillary status in patients with primary breast cancer. Physical exam carries a 29%-38% false negative rate, and radiographic methods (mammography, computed tomography, and positron emission tomography) have not achieved the level of accuracy on which to base clinical decisions [13-17]. Although complication rates may decrease by limiting the extent of axillary dissection, nondirected sampling of axillary nodes is associated with unacceptably high false negative rates: 40% for random axillary nodal sampling and 10%-15% for excision of level I nodes [18]. Recent introduction of intraoperative lymphatic mapping and sentinel lymphadenectomy (SLND) for primary breast cancer allows directed and accurate assessment of axillary involvement with minimal morbidity [19].

DEVELOPMENT OF BREAST SLND

The SLND technique was developed and first reported by Morton et al. [20] for clinical stage I cutaneous melanoma and has since been validated by independent investigators [21, 22]. This technique is based on the concept that the tumor-bearing status of the sentinel node, i.e., the first node in the regional nodal basin that drains a primary tumor, reflects the tumor status of the entire nodal basin. Our group adapted Morton’s dye-directed SLND technique for use in primary breast cancer [19].

Our initial trial was conducted during the developmental phase of adapting SLND from a cutaneous tumor system.
(melanoma) to a parenchymal tumor system (breast cancer). Sentinel nodes were detected in 114 of 174 patients (65.5%) who underwent dye-directed SLND followed by ALND [19], and the sentinel node accurately reflected axillary tumor status in 109 of 114 SLND procedures (95.6%). The 59% rate of sentinel node detection in the first 87 patients increased to 72% in the remaining 87 patients; the detection rate reached 78% by the last 50 cases in this series. However, the technique and indications were evolving. All false negatives occurred in the first 87 cases; three were caused by mistaking blue-stained fat for a sentinel lymph node. During this phase of development, the optimal amount of dye needed and the interval from dye injection to dissection were determined.

In our subsequent study of 162 patients undergoing SLND followed by completion ALND [23], frozen section examination was performed to confirm the presence of nodal tissue in the SLND specimen and to prepare for the study, in which no further axillary dissection would be performed. Immunohistochemical study (IHC) of sentinel nodes that stained negative with hematoxylin and eosin (H&E) was also introduced to increase the rate of detecting metastases. The rate of axillary metastases was 42%, compared with 29.1% in a contemporaneous cohort of 134 patients undergoing ALND alone. Thus, the SLND technique in combination with IHC staining improved axillary staging of breast cancer patients.

We then examined the accuracy of the mature SLND technique in 107 patients with T1-T2 breast cancer who underwent SLND followed by completion ALND. SLND was successful in 100 patients (93.5%). There were no false negative results, and sentinel node status was 100% predictive of axillary tumor involvement [24]. Based on the results of this study, in 1995 we stopped performing completion ALND in patients whose sentinel nodes were free of tumor cells.

Although the sensitivity and accuracy of the SLND technique validate the sentinel node concept, we undertook an exhaustive IHC assessment of 1,087 nonsentinel nodes removed from 60 breast cancer patients who had no IHC evidence of tumor cells in multiple sections of their sentinel nodes [25]. These patients were identified from a cohort of 103 consecutive breast cancer patients undergoing SLND. We identified only one tumor-positive nonsentinel node, an error rate of 0.1% (1/1,087) and an axillary status staging error rate of 0.9% (1/103). This confirms the validity of the sentinel node hypothesis in breast cancer.

Although our SLND technique is based on dye-directed intraoperative mapping, other investigators have mapped lymphatic drainage using a hand-held gamma probe and a radioactive tracer. Krag et al. [26] first described probe-directed intraoperative mapping in breast cancer using Tc-99m sulfur colloid as the tracer material. Sentinel nodes were detected in 18 of 22 patients (82%). Subsequently, Veronesi et al. [27] reported probe-directed mapping using Tc-99m-labeled human serum albumin colloid in 163 consecutive breast cancer patients who underwent SLND followed by ALND. The sentinel node was identified in 160 patients (98.2%), and its tumor status matched that of the ALND specimen in 156 patients (97.5%). Recently, Borgstein et al. [28] reported their experience with probe-directed SLND using Tc-99m labeled colloidal albumin in T1-T2 breast cancer. The sentinel node was detected in 122 of 130 patients (94%), and the technique had a sensitivity of 98%, with a false negative rate of 1.7%.

Albertini et al. [29] combined dye-directed and probe-directed mapping in 62 patients with primary breast cancer. The rate of sentinel node detection was 73% with blue dye, increasing to 92% with the additional sentinel nodes detected by probe. Sensitivity was 100% and there were no false negatives. Barnwell et al. [30] recently reported their experience with this combination approach in 42 patients undergoing SLND followed by level I/II ALND. Sentinel nodes were detected in 38 patients (90%) and were 100% accurate in predicting the tumor status of the axilla. The average number of sentinel nodes excised in the study of Albertini et al. [29] (2.2 per basin) is similar to that reported by Giuliano et al. [24] using dye alone (1.6-1.8 per basin) and to that reported by Borgstein et al. [28] and Veronesi et al. [27] using the probe alone (1.2 per basin and 1.4 per basin, respectively). This similarity underlines the fact that SLND requires only a very small specimen for accurate assessment of the axilla. It can be successfully performed in a great majority of patients with dye and/or radioactive tracer.

TECHNIQUE

The sentinel node to be excised during SLND is identified intraoperatively by lymphatic mapping using a vital blue dye and/or a radioactive tracer. In either case, the technique can be done with local anesthesia and heavy sedation, or with light general anesthesia. For dye-directed lymphatic mapping and SLND, preoperative lymphoscintigraphy is recommended if the primary tumor is in the medial quadrants, to ascertain presence of drainage to the axilla. Rarely, tumor located in the medial quadrants may drain only to lymph nodes in the internal mammary chain. Also, tumor located in the inner upper quadrant may drain directly to level III nodes.

At the time of surgery, 3-5 ml of isosulfan blue dye (Lymphazurin®) is injected into the breast parenchyma immediately adjacent to the breast mass laterally and below the subcutaneous fat, to avoid tattooing the overlying skin. If the primary tumor was excised previously, dye is injected into the wall of the biopsy cavity. If the primary tumor is not palpable,
a needle inserted under mammographic guidance for tumor localization is used to inject the dye. Approximately 5 minutes after dye injection, a transverse incision is made just below the hair-bearing area in the axilla. Blunt dissection is performed to identify the dye-filled lymphatic tract. This tract is then followed proximally and distally until a blue-stained sentinel node is identified (Fig. 1). If more than one dye-filled lymphatic tract is identified, each is followed. These tracts usually drain to the same sentinel node.

Probe-directed mapping using a radioactive tracer is performed by injecting technetium-99m (Tc-99m) labeled sulfur colloid [26] or albumin colloid [27, 28] 2-24 h prior to operation. A lymphoscintigram is obtained preoperatively to determine the axillary drainage pattern from the primary tumor (Fig. 2). At the time of surgery, a hand-held gamma-ray counter (Neoprobe® or C-Trak®) is held over the axilla to identify the area of greatest radioactivity in counts per second. A background count is established by measuring radioactivity over a neutral site. The skin is incised over the area of greatest radioactivity, and the probe is held over the incision to measure the in vivo radioactivity of axillary lymph nodes. The sentinel node is usually the node with the highest absolute count. After this node is excised, in vivo radioactivity of the axillary basin is reassessed. Some SLND investigators will continue to search for additional sentinel nodes if the absolute count of the basin still exceeds background.

Because of the difference in the radioactive tracers used, there are no uniform criteria for identifying the sentinel node by its radioactive count. Krag et al. [26] used unfiltered sulfur colloid and defined a sentinel node as any node with radioactivity three times over the background and at least 15 counts per 10 seconds. Veronesi et al. [27] used albumin colloid and defined a sentinel node as the node with the highest radioactive count. Albertini et al. [29] used sulfur colloid and defined the sentinel node as the node with >10 times the radioactivity of neighboring nonsentinel nodes; these authors also searched for additional sentinel nodes if the basin count remained 150% higher than background. Despite nonuniform definitions of a sentinel node by radioactive count, probe-directed mapping has the advantage of detecting any “hidden” sentinel node with a count higher than background. In contrast, dye-directed mapping allows surgeons to visualize the sentinel node before its excision. The blue dye technique is especially helpful when the primary tumor is close to the lymph node basin, because the radioactivity of the primary can obscure counts in the lymph node basin (shine-through effect).

**Histopathologic Analysis of Sentinel Nodes**

Because the SLND specimen contains only one or two lymph nodes, it can be routinely examined in multiple sections with IHC staining for low and intermediate molecular weight cytokeratin. This meticulous histopathologic assessment increases the sensitivity of detecting micrometastases. In our study, the 42% rate of axillary metastasis in 162 patients undergoing SLND followed by ALND was significantly ($p < 0.03$) higher than the 29.1% rate in 134 patients undergoing ALND alone [23]. The corresponding rates of axillary micrometastasis ($\leq 2$ mm) were 38.2% (26/68) and 10.3% (4/39). Eleven of the 26 micrometastases in the SLND group were identified by IHC staining after H&E stains were negative. Thus, the detailed examination of the sentinel node “upstaged” an additional 16% (11/68) of axillary lymph node basins.

Although the significance of axillary micrometastases has not been validated in a prospective fashion, several retrospective studies suggest that micrometastases are associated with poor outcome (Table 1) [31-37]. The International (Ludwig) Breast Cancer Study Group used serial sectioning of axillary lymph nodes to identify micrometastases in 9% (83/921) of breast cancer patients whose nodes were tumor-free by routine
Table 1. Studies demonstrating prognostic significance of “occult” axillary micrometastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Histologic examination</th>
<th>Incidence of occult micrometastases (%)</th>
<th>Decrease in disease-free survival associated with detection of occult micrometastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trojani et al. [31]</td>
<td>162</td>
<td>IHC</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Sedmak et al. [32]</td>
<td>45</td>
<td>IHC</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Ludwig group [33]</td>
<td>921</td>
<td>Multiple sections + IHC</td>
<td>9</td>
<td>16</td>
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<tr>
<td>Chen et al. [34]</td>
<td>80</td>
<td>IHC</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>De Mascarel et al. [35]</td>
<td>218</td>
<td>IHC</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Hainsworth et al. [36]</td>
<td>343</td>
<td>IHC</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Clare et al. [37]</td>
<td>86</td>
<td>Multiple sections + IHC</td>
<td>13</td>
<td>28</td>
</tr>
</tbody>
</table>

IHC = immunohistochemical staining. *Length of follow-up varies.

Table 1. Studies demonstrating prognostic significance of “occult” axillary micrometastases

histopathological examination [33]. Patients with micrometastases had lower rates of five-year disease-free survival \( (p = 0.0003) \) and overall survival \( (p = 0.002) \) than those whose nodes remained negative: 58% and 79%, respectively, versus 74% and 88%, respectively. Two subsequent large \( (n > 100) \) retrospective analyses also demonstrated the prognostic importance of identifying occult micrometastases when H&E stains are negative. De Mascarel et al. [35] used IHC to identify micrometastases in 50 of 218 patients (23%) whose ALND specimens stained negative for tumor cells with H&E. In patients with invasive ductal carcinoma, IHC-detected micrometastases were the most significant factor associated with recurrence (multivariate \( p \)-value = 0.011). Although IHC-detected micrometastases were not significant for survival in this subset of patients on univariate analysis (\( p = 0.07 \)), they were significant on multivariate analysis (\( p = 0.027 \)). Hainsworth et al. [36] identified occult metastases in 41 of 343 “node negative” patients (12%) whose nodal specimens were reexamined with IHC. The presence of occult metastases increased the five-year recurrence rate from 16% to 32%. A prospective study of the significance of IHC-detected occult metastases will be conducted by the American College of Surgeons.

**CONCLUSION**

Since only about one-third of patients with a clinically negative axilla have nodal metastases after histopathological examination of the ALND specimen [13, 36-40], a significant number of patients would be at risk for the morbidity of ALND without benefiting from the procedure. The likelihood of a tumor-positive node in a clinically negative axilla is even lower for patients with small lesions [41-44]. Furthermore, axillary status does not affect the selection of adjuvant therapy in approximately 40% of patients [45, 46], although it provides important prognostic information. With minimal risk of complications, SLND can accurately distinguish patients who would not benefit from ALND from those who would benefit from a complete axillary staging with ALND. However, SLND should be considered as an experimental technique because its clinical efficacy has only been demonstrated in relatively small trials. Furthermore, although some authors had not noted “learning curve” in this procedure, any breast surgeon undertaking SLND should perform completion ALND until the former technique is mastered. Quality control is paramount for successful application of this technique as an adjunct for management of breast cancer. Not uncommonly, the sentinel node is the only lymph node containing tumor cells. In our previous study of 107 consecutive patients [24], 67% (28/42) of those with sentinel node involvement had no other tumor-positive nodes in the axillary basin. Corresponding rates of 40% (32/81), 59% (26/44), 67% (12/18), and 33% (5/15) have been reported by Veronesi et al. [27], Borgstein et al. [28], Albertini et al. [29], and Barnwell et al. [30], respectively. However, there is no accurate means of predicting which patients will have axillary metastasis limited to the sentinel node. Therefore, completion ALND should be performed in all patients with positive sentinel nodes to accurately assess the degree of axillary nodal involvement.

Since no other less morbid procedure approaches the diagnostic accuracy of ALND in terms of assessing axillary nodal status, the importance of SLND as an axillary staging technique in breast cancer merits evaluation in a multicenter prospective trial. However, issues regarding consensual definition of sentinel node by the radioactive tracer technique, kinetics of the different radioactive tracers, and quality control of SLND technique in the community must be resolved.

**ACKNOWLEDGMENTS**

Supported in part by funding from the Ben B. and Joyce E. Eisenberg Foundation, Los Angeles, California, and the Fashion Footwear Association of New York.
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