Radio-guided Sentinel Lymph Node Biopsy Using Periareolar Injection Technique for Patients with Early Breast Cancer

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Background/Purpose: Sentinel lymph node (LN) biopsy has been widely adopted in the axillary staging of clinical node-negative breast cancer patients. This study aimed to evaluate the accuracy of radio-guided sentinel LN (SLN) biopsy (SLNB) using the periareolar injection technique for predicting the histopathologic status of axillary LNs in early breast cancer patients.

Methods: Between November 2003 and November 2004 in the National Taiwan University Hospital, radio-guided SLNB using the periareolar injection technique was consecutively performed in 213 female patients with early breast cancer (stage T1 and T2) but without clinically palpable axillary LN and previous chemotherapy. Two mCi of filtered (0.22 μm) 99mTc-sulfur colloid were injected in the afternoon 1 day before surgery (2-day protocol) or 1 mCi of the same radiopharmaceutical was injected on the morning of the surgery (1-day protocol). During surgery, a handheld gamma probe was used to identify the LNs with radioactivity in the axilla. A node was deemed a SLN if its radioactivity was >10% of the hottest node. All the SLNs identified were removed for histology.

Results: Radioactive SLN was identified at surgery in 207 patients. The SLN identification rate was 97.2% (207/213). Of these 207 patients, 163 patients had received both SLNB and axillary LN dissection. Among these 163 patients, 77 patients had LN metastases and four had negative SLN but positive non-SLN. The false-negative rate of SLNB for the detection of axillary LN metastases was 5.2% (4/77). There were no statistical differences between false-negative and SLN positive groups for all factors.


Key Words: breast cancer, periareolar injection, sentinel lymph node biopsy, 99mTc radiocolloid

Axillary lymph node (LN) involvement is the most important independent prognostic factor for breast cancer.1,2 Postoperative adjuvant systemic therapy is regularly indicated for patients with positive axillary LN metastasis.3 Until recently, axillary LN dissection (ALND) has been the standard surgical procedure to determine the axillary LN staging for this type of patient. However, early and long-term complications such as seroma formation, sensory changes, lymphedema and chronic pain, have been observed frequently in the ipsilateral arm of patients with ALND.
Lately, sentinel LN biopsy (SLNB) has been widely adopted in the axillary staging for clinical node-negative breast cancer patients.4−8 Sentinel LN (SLN) is defined as the first LN on the direct lymphatic pathway draining from a tumor.9,10 It has been generally accepted that the status of the SLN is able to accurately predict the histopathologic status of the regional lymphatic basin.11 If the SLN is free of tumor metastasis, it is usually expected that the tumor will not spread to the at-risk regional lymphatic basin and ALND for the patient is unnecessary.5

There are various techniques for SLN identification and localization. They vary according to the material used, such as blue dye or radioisotope-labeled colloid,12−17 and according to the site of injection, such as peritumoral, subdermal18−20 or sub/periareolar.21−25 The objective of this study was to evaluate the accuracy of radio-guided SLNB using the periareolar injection technique for predicting the histopathologic status of axillary LN in early breast cancer patients in our hospital.

Patients and Methods

Patients

Between November 2003 and November 2004 in the National Taiwan University Hospital, radio-guided SLNB using the periareolar technique was performed in 213 consecutive female patients (mean age, 50.3 ± 11.1 years; range, 24–83 years) with early breast cancer (stage T1 and T2; mean tumor size, 2.4 ± 1.2 cm) and clinically non-palpable axillary LN, and without previous chemotherapy. Preoperative diagnoses of breast cancer for these 213 patients were established on either cytology of fine-needle aspiration or histology of core or excisional biopsy specimens. Informed consent was obtained from each patient.

Lymphoscintigraphy

Each patient had intradermal periareolar injection in the quadrant where the tumor was located. Two mCi of filtered (0.22 μm) ⁹⁹ᵐTc-sulfur colloid were injected in the afternoon 1 day before surgery (2-day protocol) or 1 mCi of the same radiopharmaceutical was injected on the morning of surgery (1-day protocol).

Images were acquired using large-field-of-view gamma cameras equipped with low energy high resolution collimators. Imaging was performed in anterior projection or both anterior and lateral projections while the patient’s arm extended toward the head for maximal axillary exposure. To improve on anatomic detail, a cobalt 57 flood source was placed behind the patient for a transmission scan. The images were taken every 30 minutes until tracer activity could be identified in the axillary regions. The skin directly over the SLN(s) was then marked with a surgical skin marker to locate the SLN(s) during surgery.

SLNB

During surgery, a handheld gamma probe (Navigator GPS; US Surgical Corp., Tyco Healthcare Group, Norwalk, CT, USA) was used to identify the LNs with radioactivity in the axilla. A node was deemed to be a SLN if its radioactivity was > 10% of the hottest node. All the SLNs identified were then removed for histology. The biopsy sites were re-examined after harvesting the SLNs to ensure that all radioactive LNs had been removed. A routine level I and II ALND was subsequently performed after SLNB in 163 patients.

Pathologic evaluation

A series of sections for each LN embedded in a paraffin block were examined using hematoxylin and eosin as well as immunohistochemical staining with anti-cytokeratin antibodies.

Statistical analysis

All data are expressed as mean ± standard deviation. Comparisons between different groups were performed using two-tailed paired and unpaired Student’s t tests. Statistical analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC, USA) for Windows. Logistic regression was used to evaluate the relative risk between two groups. The sentinel node identification rate was defined as the ratio of the number of patients
with detected SLN over the total number of patients that were injected with 99mTc-sulfur colloid. The axillary metastatic rate was calculated by dividing the number of patients with axillary metastasis by the number of patients enrolled in the study. Patients with negative sentinel node but with positive axillary metastases in one or more of the non-sentinel LNs (NSLNs) were identified as having a false-negative result. The false-negative rate was defined as the number of false-negative patients divided by the total number of patients with metastases in either SLN or NSLN.

**Results**

**Patients**

A total of 213 patients received intradermal peri-areolar injections of filtered 99mTc-sulfur colloid. Radioactive SLNs were not identified at surgery in six of the 213 patients who received SLNB. The SLN identification rate in this study was therefore 97.2% (207/213). The patients’ characteristics are shown in Table 1. The mean age of the six patients with failed SLNB was slightly higher than that of the 207 patients with successful SLNB (58.3 ± 22.5 vs. 50.1 ± 10.6), but the difference was not statistically significant ($p = 0.4159$). For these six patients, 50% (3 patients) had received excisional biopsies before SLNB, 33% (2 patients) were later discovered to have axillary LN metastases by ALND and 50% (3 patients) underwent the 1-day protocol. There were no statistically significant differences between “successful SLNB” and “failed SLNB” patients for all factors including previous excisional biopsies, positive axillary metastases and 1-day protocol.

Of the 207 patient whose SLNs were identified successfully, 44 had elected SLNB and not to undergo ALND because of negative LN.

**Pathologic results for patients who received both SLNB and ALND**

The remaining 163 patients, who underwent both SLNB and ALND successfully, were included in the data analysis. The accuracy of SLNB was examined by comparing the histopathology of SLN and NSLN. Table 2 summarizes the results. There were 73 patients with SLN metastases; the SLN metastatic rate was 44.8% (73/163). There were 77 patients with LN metastases in SLN, axillary NSLN, or both; the axillary metastatic rate was 47.2% (77/163). Forty-four patients (57.1%) had positive SLN but no tumor involvement of NSLN.

**Table 1.** Profiles of the 207 patients with successful sentinel lymph node biopsy (SLNB) and six patients with failed SLNB*

<table>
<thead>
<tr>
<th></th>
<th>Successful SLNB</th>
<th>Failed SLNB</th>
<th>$p$</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>207</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>$50.1 \pm 10.6$</td>
<td>$58.3 \pm 22.5$</td>
<td>0.4159</td>
</tr>
<tr>
<td>Primary tumor size (cm)</td>
<td>$2.3 \pm 1.2$</td>
<td>$2.8 \pm 1.7$</td>
<td>0.3944</td>
</tr>
<tr>
<td>Previous excisional biopsy</td>
<td>47 (23)</td>
<td>3 (50)</td>
<td>0.1199</td>
</tr>
<tr>
<td>Positive axillary basins</td>
<td>77 (37)</td>
<td>2 (33)</td>
<td>0.8568</td>
</tr>
<tr>
<td>1-day protocol</td>
<td>78 (38)</td>
<td>3 (50)</td>
<td>0.5400</td>
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</table>

*Data are presented as mean ± standard deviation or n (%).

**Table 2.** Pathologic lymph node results for the 163 patients who received both sentinel lymph node biopsy and axillary lymph node dissection

<table>
<thead>
<tr>
<th>Final pathology (including SLN and NSLN)</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
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<tbody>
<tr>
<td>SLN</td>
<td>73</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Positive</td>
<td>73</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>86</td>
<td>163</td>
</tr>
</tbody>
</table>

SLN = sentinel lymph node; NSLN = non-sentinel axillary lymph node.
and four patients had negative SLN but positive tumor involvement in NSLN. The sensitivity, specificity, negative predictive value and false-negative rate of SLNB for the detection of axillary lymph node metastases were 94.8% (73/77), 100% (86/86), 95.6% (86/90) and 5.2% (4/77), respectively.

The patients’ characteristics, which include age, primary tumor size, number of SLN examined, number of NSLN examined, cases with previous excisional biopsy, and cases with 1-day protocol, are presented in Table 3 under the “false-negative” and “SLN-positive” columns. There were no statistical differences between these two columns for all factors corresponding to rows in Table 3.

Among the 73 patients whose SLNs were identified as positive for metastasis, 62 showed positive results for their hottest SLN; seven patients were found to have negative results for their hottest SLN but positive results for their second hottest SLN; four patients were found to have positive results beginning from their third hottest SLN.

Comparison between 1-day and 2-day protocols

The comparison between 1-day and 2-day protocols is illustrated in Table 4. Sixty-four patients underwent SLNB using the 1-day protocol and the remaining 99 patients adopted the 2-day protocol for their SLNB. The two groups differed significantly in the age category (47.5 ± 9.1 vs. 52.4 ± 11.3; \( p = 0.0041 \)), but not in the categories of the number of SLN examined, the number of cases with LN metastases and false-negative rates. The 1-day protocol was usually adopted for afternoon surgery while the 2-day protocol was adopted for morning surgery. In our hospital, the elderly patients were, by courtesy, usually scheduled for surgery in the early morning. Therefore, the mean

<table>
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<th>Table 3. Profiles of the four patients with false-negative sentinel lymph node (SLN) and 73 patients with positive SLN*</th>
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<tr>
<td>False-negative</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Primary tumor size (cm)</td>
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<tr>
<td>Number of SLN examined</td>
</tr>
<tr>
<td>Number of NSLN examined</td>
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<tr>
<td>Cases with previous excisional biopsy</td>
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<tr>
<td>Cases with 1-day protocol</td>
</tr>
<tr>
<td>*Data are presented as mean ± standard deviation or n (%). NSLN = non-sentinel axillary lymph node.</td>
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<th>Table 4. Comparison between 1-day and 2-day protocols*</th>
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<td>1-day protocol</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
</tr>
<tr>
<td>Number of SLN examined</td>
</tr>
<tr>
<td>Number of NSLN examined</td>
</tr>
<tr>
<td>Cases with LN metastases</td>
</tr>
<tr>
<td>Number of false-negative cases</td>
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<tr>
<td>False-negative rate (%)</td>
</tr>
<tr>
<td>*Data are presented as mean ± standard deviation or n (%); (^1)p &lt; 0.05. SLN = sentinel lymph node; NSLN = non-sentinel axillary lymph node; LN = lymph node.</td>
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</table>
age of patients in the 2-day protocol group was higher than that of the 1-day protocol group.

**Lymphoscintigraphy**

Lymphoscintigraphy was performed for all patients using the intradermal periareolar injection technique. Clear focal accumulation of radioactivity was visible at the ipsilateral axilla in 206 of 213 lymphoscintigraphic images (96.7%); three of these 206 patients failed SLNB. Among the seven patients whose lymphoscintigraphy failed to reveal obvious nodal uptake in the ipsilateral axilla, four were identified to have radioactive SLN at surgery using more sensitive handheld probes. Internal mammary (IM) drainage was noted in two patients of the total 213 patients under study; the IM visualization rate was 0.9% (2/213).

**Discussion**

Since its introduction in the mid 1990s, SLNB has been widely adopted for axillary staging in patients with early breast cancer. Although numerous SLNB techniques that vary on the choice of localizing agent(s), the particle size of the agent, timing of injection, and site of injection have been utilized, a recent meta-analysis found that the results of SLNB do not vary significantly among these different techniques and are generally in agreement with results from ALND.26 The pattern of lymphatic drainage of the breast is unique. It travels centripetally to the subareolar plexus and then to the axilla via lymphatic collecting channels. This was first described by Sappey and affirmed by many studies thereafter.27 It has now been widely accepted that tumors of the breast, regardless of location, drain through a common afferent lymphatic channel to a common axillary SLN. This is likely to be the reason that the same SLN is identified by peritumoral or periareolar injection of blue dye or radiocolloid.28−32

The periareolar injection technique has several advantages over other techniques.

1. It does not require accurate injection site and is relatively easy to perform.
2. Since the tracers are efficiently and rapidly taken up by the dense subareolar plexus, SLN is more rapidly visualized in the axilla.25 As the percentage of tracer reaching the SLN is higher when injected via the periareolar route than via the subdermal/peritumor route, it is easier to identify SLN by periareolar injection than by subdermal/peritumor injection.
3. For patients with non-palpable tumor, the periareolar approach dispenses with image-guided injection.28
4. It is possible to perform SLNB in patients with multicentric tumors using the periareolar injection technique.33−34
5. For a tumor located in the outer upper quadrant of the breast, periareolar injection, which increases the distance between the injection site and axillary SLN, reduces the shine-through effect.7

In view of the above advantages, we have adopted periareolar injection of radiolabeled tracer to localize SLN in our hospital. It has been reported that IM SLN could not be identified by periareolar injection.35 In this study, only two IM drainages were noted out of the total of 213 cases. Although IM SLNB is feasible, patients with positive IM nodes but negative axillary nodes are rare. The impact of determining IM LN status on patient management, disease-free and overall survival has not yet been established.36 At present, IM SLNB is not routinely performed in our hospital.

The SLN identification rate in this study was 97.2% (207/213), and the false-negative rate was 5.2%. Although Schrenk et al reported that the accuracy of SLNB did not increase with more SLN removals,36 our study nevertheless shows that the number of false-negative cases would be increased to eight (10.4%) if we only excised the first two hottest SLNs for the 77 positive SLN patients in our study. This is in agreement with the suggestion in previous studies to completely excise all radioactive SLNs to reduce the false-negative rate.13,16

Previous studies suggest that the optimal interval between injection and SLNB is from 30 minutes to 24 hours.7,8,37−40 Recently, Chua et al proposed that the optimal interval between injection and
surgery is in the range of 20–300 minutes. Our results show no difference in the number of SLNs harvested and the false-negative rates between patients under the 1-day protocol (interval of 1–6 hours) and patients under the 2-day protocol (interval of 16–20 hours). The 2-day protocol has the advantages of high SLN-to-background and significantly low radioactivity in the resected specimen relative to the 1-day protocol.

Conclusion

Our study suggests that SLNB with periareolar injection of radiocolloid and gamma probe-guided technique is a simple and effective procedure for SLN sampling in patients with early breast cancer. The SLNB result provides accurate and useful information on the status of axillary nodes.

Acknowledgments

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References


