Roles of Preoperative Lymphoscintigraphy for Sentinel Lymph Node Biopsy in Breast Cancer Patients

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Objective: To evaluate roles of preoperative lymphoscintigraphy for sentinel lymph node biopsy in breast cancer patients.

Methods: Five hundred and sixty-five consecutive breast cancer patients were prospectively randomized into groups with or without preoperative lymphoscintigraphy.

Results: In a group with lymphoscintigraphy, 238 patients had sentinel lymph nodes spotted in lymphoscintigram. The visualization of sentinel lymph nodes in lymphoscintigram was not associated with patients’ age, primary tumor size and location, histopathologic type and time interval from injection of radiocolloid to lymphoscintigraphy. However, patients with axillary metastasis had a lower identification rate of sentinel lymph nodes by lymphoscintigraphy than those without metastasis (P = 0.003). The identification rate of axillary sentinel lymph nodes was 99.3% in the group and the rate was similar whether there was sentinel lymph nodes spotted in axillary lymphoscintigram or not (99.6% vs. 98.1%, P = 0.327). The false-negative rate in this group was 4.2%. While in a group without lymphoscintigraphy, the identification rate and the false-negative rate were 99.6% and 4.8%, respectively. There was no significant difference between the two groups in the identification rate of axillary sentinel lymph nodes (P = 0.594) and in the false-negative rate (P = 1.00).

Conclusion: Preoperative lymphoscintigraphy could neither improve the identification rate nor reduce the false-negative rate of breast cancer sentinel lymph node biopsy, and it is not necessary for sentinel lymph node biopsy in breast cancer patients.

Key words: breast cancer – sentinel lymph node biopsy – lymphoscintigraphy

INTRODUCTION

The status of axillary lymph nodes is one of the most important prognostic factors in breast cancer (1,2), and sentinel lymph nodes (SLNs) can accurately predict the status of axillary lymph nodes in clinical node-negative breast cancer patients (3–6). Currently, sentinel lymph node biopsy (SLNB) has become a common procedure for early breast cancer patients, and it provides accurate axillary staging while sparing node-negative patients the morbidity associated with axillary lymph node dissection (ALND).

SLNB was first widely performed in the management of melanoma. In melanoma, the lymph drainage was variable and usually far from the primary tumor site. Preoperative lymphoscintigraphy could provide a wide field of view in locating SLNs. Therefore, it was widely performed in the SLNB of melanoma (7,8). When the SLNB technique was introduced into the staging and treatment of breast cancer, preoperative lymphoscintigraphy was introduced accordingly. However, the lymph drainage of breast was relatively confined to the axilla. Furthermore, most surgeons did not remove extra-axillary nodes routinely. Although preoperative lymphoscintigraphy was frequently undergone when isotope-labeled tracer was injected, its roles remained controversial.
Thus, the aim of this study was to evaluate roles of preoperative lymphoscintigraphy for SLNB in breast cancer patients. Considering that identification rate and false-negative rate are the most important factors in SLNB, we mainly focused on the relationship between preoperative lymphoscintigraphy and these two factors.

PATIENTS AND METHODS

PATIENTS

From July 2007 to November 2009, 565 consecutive breast cancer patients scheduled for SLNB were prospectively randomized into two groups: 290 patients were randomized into Group 1 that lymphoscintigraphy was done before SLNB and 275 patients were randomized into Group 2 without preoperative lymphoscintigraphy. SLNs of these enrolled patients were identified by a combination of $^{99m}$Tc-labeled sulfur colloid ($^{99m}$Tc-SC) and blue dye. The study was approved by the ethics committee and each patient provided informed consent. Patients with previous ipsilateral axillary surgery or those who received neoadjuvant chemotherapy before surgery were excluded from this study.

PREOPERATIVE LYMPHOSCINTIGRAPHY

Sulfur colloid was labeled by $^{99m}$Tc after filtering through a millipore filter of 220 nm pore size. $^{99m}$Tc-SC ranging from 7.2–37.0 MBq, in 0.5–2.0 ml, was injected subcutaneously above the primary tumor or around the biopsy cavity on the day before surgery or at least 4 h on the surgery day. Sequential anterior and lateral gamma imaging was performed with patients lying prone and by injection side just before surgery using a digital gamma camera computer system (Toshiba GCA-901A/HG). The hot spots outside the injection site were identified as SLNs.

IDENTIFICATION OF SLNs

We identified SLNs by combining the use of intraoperative gamma detector (Neoprobe, Neo2000 gamma detection system, Johnson and Johnson) and blue dye. Four milliliters of 1% of methylthioninium was injected subcutaneously above the primary tumor or around the biopsy cavity 10 min before surgery. Lymph nodes with blue lymphatic vessel directly leading to them (SLNs by blue dye) and those with radioactivity count higher than 10% of the highest radioactivity count of lymph node (SLNs by isotope) were regarded as SLNs.

SURGERY

Sixty of 290 patients in Group 1 and 55 of 275 in Group 2 did not agree with SLNB substituting for ALND, and they underwent ALND following SLNB despite of the status of SLNs. We call this group of patients the verifying group with which we can evaluate the false-negative rate. Otherwise, patients underwent only SLNB if SLNs were negative and ALND was performed consequently if SLNB was failure or SLNs were positive.

STATISTICAL METHODS

Chi-square test or Fisher’s exact test was performed to compare the rate between different groups, and $t$-test was used to compare the difference of means between groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

Patients in Group 1 and Group 2 were well balanced in terms of the age of patients, the stage, histopathologic type, location of primary tumor, time interval from injection of radiocolloid to lymphoscintigraphy and axillary metastasis status (Table 1).

In Group 1, 238 patients (82.1%) had SLNs spotted in lymphoscintigram, and internal mammary SLNs were found in 4 (1.7%) patients by lymphoscintigraphy. As Table 1 shows, the visualization of SLNs in lymphoscintigram was not associated with patients’ age, primary tumor size and location, histopathologic type and time interval from injection of radiocolloid to lymphoscintigraphy. However, patients with axillary metastasis had a lower identification rate of SLNs by lymphoscintigraphy than those without metastasis ($P = 0.003$). The identification rate of axillary SLNs was 99.3% (288 of 290) in the group and the rate was similar whether there was SLNs spotted in axillary lymphoscintigram or not [99.6% (1 of 237) vs. 98.1% (1 of 52), $P = 0.327$]. There was 1 false-negative result of SLNB among 24 patients whose SLNs were surgically removed and the axillary nodes were positive in the verifying group, and the false-negative rate was 4.2%.

In Group 2, the identification rate and the false-negative rate were 99.6% (274 of 275) and 4.8% (1 of 21), respectively. There was no significant difference between the two groups in the identification rate of axillary SLNs ($P = 0.594$) and in the false-negative rate ($P = 1.00$).

DISCUSSION

Breast cancer SLNB is often performed using the tracer of isotope, blue dye or both of them. When using isotope, preoperative lymphoscintigraphy is often performed in many institutions. To evaluate whether preoperative lymphoscintigraphy was a prerequisite for SLNB, we should not only make it clear whether it is associated with improved identification rate and decreased false-negative rate, but also find out whether it is necessary in finding SLNs.

Some previous articles concluded that the identification rate of axillary SLN with preoperative lymphoscintigraphy was superior to the rate by that without ($9,10$). In our study, we demonstrated that there was no significant difference in
the identification rate of axillary SLNs whether preoperative lymphoscintigraphy was done or not. Moreover, the identification rate was similar whether there was SLNs spotted in axillary in lymphoscintigram or not. Even in patients with no SLN spotted in axillary in lymphoscintigram, the identification rate of axillary SLNs reached to 98.1% by a combination of intraoperative gamma detector and blue dye. Previous studies also reported that SLNs was identified in about 78–93% of patients in whom preoperative lymphoscintigraphy failed to spot SLNs (10–16). Therefore, we concluded that there would be still high identification rate of axillary SLNs even preoperative lymphoscintigraphy was not done, and failure in identification of SLNs by lymphoscintigraphy did not predict the failure of SLNB.

Due to its disadvantage in anatomic structure image, lymphoscintigraphy is not suitable for anatomy localization. Therefore, lymphoscintigraphy could provide limited information to facilitate locating SLNs intraoperatively. The hand-held gamma probe with collimator has a narrow view field, which is necessary to locate the radio source accurately. Moreover, even equipped with a low-energy, high-resolution collimator, the sensitivity of gamma camera is still lower than the hand-held gamma detector. It was reported that combining the use of isotope and blue dye could improve the identification rate of SLNs intraoperatively (5,17–19). We also thought that if SLNs were not visualized in lymphoscintigram, the addition of intraoperative blue dye was recommended to increase the likelihood of SLNs identification.

False-negative rate is another important factor in performing SLNB in breast cancer. Our results showed that there was no significant advantage with respect to false-negative rates in patients with preoperative lymphoscintigraphy when compared with those without. This observation was consistent with the previous published results (10,11).

The wide view field of lymphoscintgram can provide helpful information for the identification of extra-axillary SLNs. In our retrospective study, we found that 1.7% of patients had visualized SLNs in internal mammary. Previous studies revealed that 2–45% patients had internal mammary SLNs in lymphoscintgram and superficial or subcutaneous injections above the primary tumor had a lower chance of showing internal mammary drainage than peritumoral injections (13,20–25). However, there were arguments on the treatment of internal mammary nodes. Some (26–28) thought that dissection of internal mammary nodes benefited only a small portion of breast cancer patients, and it would result in more injuries to these patients and lead to more complications. While others (29–30) gave the opposite opinion, and they argued that therapy was altered in a substantial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
<th>Visualized SLNs in Group 1</th>
<th>Nonvisualized SLNs in Group 1</th>
<th>P value</th>
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<tbody>
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<td>Histology</td>
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<td>Noninvasive carcinoma</td>
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<td>0.719</td>
<td>46.6 years</td>
<td>46.3 years</td>
<td>0.874</td>
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proportion of patients by internal mammary SLNB and survival was worse in patients who had internal mammary drainage ignored when planning adjuvant therapy. We believe that it is necessary to design large clinical trials to explore the value of internal mammary SLNB further. Before the results turn out, it should not be recommended as a standard procedure in clinical practice. However, it should be specifically pointed out that internal mammary nodes could also be detected by intraoperative gamma detector instead of preoperative lymphoscintigraphy.

Based on the present results, we could draw the conclusion that preoperative lymphoscintigraphy could not improve the identification rate and reduce the false-negative rates of breast cancer SLNB, and it is not necessary for SLNB in breast cancer patients.

Conflict of interest statement
None declared.

References