—Report on Experiments and Clinical Cases—

Evaluation of Sentinel Lymph Node Biopsy in Clinically Node-Negative Breast Cancer

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Abstract

Background: In patients with clinically node-negative breast cancer, diagnosed with palpation and several types of imaging examination, sentinel lymph nodes accurately predict the status of the other axillary nodes, which determine the nature of subsequent adjuvant treatment. In addition, compared with axillary lymph node dissection, sentinel-node biopsy results in less postoperative morbidity, including pain, numbness, swelling, and reduced mobility in the ipsilateral arm.

Methods: We analyzed the validity of the sentinel node biopsy procedure using dual-agent injection of blue dye and radioactive colloid performed in our hospital from May 2006 through March 2010. A total of 258 breasts of 253 patients were studied. Simultaneous axillary lymph node dissection was performed only if rapid intraoperative diagnosis identified metastasis in sentinel lymph nodes. The identification rate, accuracy, provisional false-negative rate, which was calculated with data from all 65 patients whose sentinel lymph nodes had metastasis, and axillary recurrence rate of sentinel node biopsy were calculated.

Results: The sentinel node identification rate was 99.2%, and the accuracy of sentinel lymph node status was 98.0%. The provisional false-negative rate was 7.7%. During an observation period averaging 24 months, axillary recurrence was observed in only 1 of 256 cases (0.4%), and there were no cases of parasternal recurrence. In patients who underwent sentinel-node biopsy without axillary lymph node dissection, there was no obvious morbidity.

Conclusion: Our sentinel-node biopsy procedure yielded satisfactory results, which were not inferior to the results of previous clinical trials. Thus, we conclude our sentinel-node biopsy procedure is feasible. If the efficacy and safety of sentinel-node biopsy are confirmed in several large-scale randomized controlled trials in Europe and the United States, sentinel-node biopsy will become a standard surgical technique in the management of clinically node-negative breast cancer.
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Key words: breast cancer, sentinel lymph node, sentinel-node biopsy, sentinel lymph node biopsy

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Introduction

Axillary lymph node status is an important prognostic factor in breast cancer which determines the nature of subsequent adjuvant treatment[1]. However, reports indicate that axillary lymph node dissection (ALND) results in postoperative morbidities, including pain, numbness, swelling, and reduced mobility in the ipsilateral arm[23].

On the other hand, patients who undergo only sentinel node biopsy (SNB) have less postoperative morbidity than do patients who undergo ALND[23]. Findings from sentinel lymph nodes (SNLs) could accurately predict the status of the other axillary lymph nodes in clinically node-negative breast cancer[4]. SNB is performed in some countries, despite limited data from randomized trials on morbidity and mortality outcomes[5,6].

A standard protocol for SNB has not been established. In our hospital, we have performed SNB since 2005 for patients with early breast cancer. Initially, a dye-guided method[7] was used. Previously, we performed a feasibility study using findings from back-up ALND, and qualified ourselves to omit ALND after SNB on the basis of criteria described in a previous report[8]. We introduced an SNB method using dual-agent injection of blue dye and radioactive colloid in May 2006. In the present study, we analyzed the validity of this dual-guided SNB procedure now performed in our hospital.

Materials and Methods

Patients

The study comprised 258 breasts (i.e., 258 cases) of 253 patients who underwent surgery for primary breast cancer at our hospital from May 2006 through March 2010. The clinical diagnosis for all patients was node-negative breast cancer (Tis or T1-3, N0, M0)[9]. The 258 cases included 2 cases in men, 5 cases of multifocal breast cancer (i.e., multiple cancers in the same breast quadrant), and 4 postexcisional biopsy cases. We excluded patients who had received neoadjuvant chemotherapy and those in whom cancer had recurred in the same

breast.

Written informed consent was obtained from all patients, and the study was approved by the institutional review board of the hospital. In October 2008, we joined a multicenter-based phase II study of the safety of SNB for primary breast cancer without axillary lymph node metastasis[10].

The Combined SNB Procedure

Dual-agent SLN mapping was performed as follows: 3.0 to 7.4 MBq of technetium-99m-labeled particles of phytic acid in 1 mL of saline was injected into the intracutaneous region of the areola 2 to 19 hours before surgery. Preoperative lymphoscintigraphy (LS) was performed 2 to 3 hours after radiotracer injection. The blue dye used was 1 to 2 mL (4−8 mg) of indigo carmine (Daiichi-Sankyo Co. Ltd., Tokyo, Japan). The dye was injected without massage at an intracutaneous site above the tumor when the tumor was located mainly in the C area[9] or was injected at the areola if the tumor was located mainly in other areas. The gamma probe (GP) used was the Navigator GPS (Covidien Japan Inc., Tokyo, Japan).

Rapid intraoperative pathological examinations used 2-mm-thick frozen sections stained with hematoxylin and eosin. Final pathological diagnostic examinations were performed postoperatively with permanent formalin-fixed, paraffin-embedded sections stained with hematoxylin and eosin.

Simultaneous ALND was performed only if a rapid intraoperative diagnostic examination identified metastasis in SLNs. Because we discontinued back-up ALND, we were unable to calculate the exact false-negative rate. Instead, the provisional false-negative rate was calculated using data from all 65 patients whose SLNs had metastasis. A false-negative case was defined as one in which metastasis was not identified with intraoperative examination, but macrometastasis was subsequently detected on final diagnostic examination. Cases were not classified as false negatives if intraoperative diagnostic examination returned a negative result for SLN metastasis, but only micrometastasis[9] was subsequently detected on examination of permanent sections.

Table 1   The results of SNB in this study

| | | Metastasis in Axillary Lymph Nodes | | Total |
		Positive	Negative	
Metastasis in SLNs	Positive	60	0	60
	Negative	5	191	196
Total		65	191	256

Provisional false negative rate = 7.7% (5/65)
Accuracy = 98.0% (251/256)

Patients with false-negative results and the physician-in-charge discussed treatment options, which included 2-stage ALND, postoperative axillary radiation, and postoperative chemotherapy.

Results

The SLN identification rate was 99.2% (256 of 258 cases). The average number of SLNs was 1.8 (range, 1–7). All SLNs were detected in the axilla. The assessment of SLN status had an accuracy rate of 98.0% (251 of 256 cases), and the provisional false-negative rate was 7.7% (5 of 65 cases) (**Table 1**). Metastasis was detected only in SLNs in 58.5% of cases (38 of 65 cases).

The rate at which only micrometastasis was observed in permanent SLN sections was 3.5% (9 of 256 cases). In 2 of these 9 cases, metastasis had not been detected with intraoperative diagnostic examination.

During an observation period averaging 24 months, axillary recurrence was observed in only 1 of 256 cases (0.4%), and there were no cases of parasternal recurrence.

Patients who underwent SNB without ALND had no obvious morbidity.

The findings of SLN types in the 256 cases were classified as follows: 167 cases of hot and blue nodes only, 27 cases of hot and gray nodes only (including 7 metastasis-positive cases), and 0 cases of cold and blue nodes only.

Preoperative LS was performed in 189 of 256 breasts (cases) (183 of 248 patients). The sensitivity of LS was 100.0% when cases with more than 1 hot node were defined as positive. The differences in the number of hot nodes detected with LS versus that detected with GP were as follows: 1) LS=GP: 66.1% (125 of 189 cases); 2) LS>GP: 5.3% (10 cases); and 3) LS<GP: 28.6% (54 cases).

There were only 2 patients in whom SLNs could not be identified. The first patient was a 49-year-old woman with breast cancer (T2, N0, M0)[9]. Her height was 177 cm, body weight was 98 kg, and the body mass index (BMI) was 31.3 kg/m^2. LS revealed weak uptake in the axilla, but no SLNs were identified with GP. She underwent total mastectomy and ALND (level I/II)[9]. The final pathological diagnosis was pN1[11] (2 of 18). The second patient was a 64-year-old woman with breast cancer (T1c, N0, M0)[9]. Her height was 148.5 cm, body weight was 54.4 kg, and BMI was 24.7 kg/m^2. No SLNs were identified with either LS or GP. She underwent total mastectomy and ALND (level I)[9]. The final pathological diagnosis was pN1[11] (1/7).

The single case of axillary recurrence was in an 83-year-old woman with breast cancer (T2, N0, M0)[9]. LS indicated 1 hot signal in the axilla, and GP identified 1 hot and blue node. The intraoperative pathological examination found no metastasis in the SLN. The patient underwent partial mastectomy[9] and sampling of axillary nodes. The final pathological diagnosis was pT2, pN0[11] (sn 0/1, level I 0/3), ly1, v0, negative surgical margin[9]. She declined any adjuvant therapy. A mass was detected with palpation and ultrasonography in the right axilla 6 months after surgery. Fine-needle aspiration cytologic examination revealed malignant cells. She underwent right ALND (level I/II) 8 months after surgery. Pathological analysis revealed lymph node metastasis from breast cancer; n 8/17 (level I 8/15, level II 0/2)[9]. Postoperative hormonal therapy was administered after the second ALND. There has

been no sign of recurrence in the 40 months since the second surgery.

Discussion

An indication for SNB is clinically node-negative (N0) breast cancer. The diagnosis of N0 is established by palpation and several imaging examinations, including ultrasonography, computed tomography (CT), multidetector-row CT, magnetic resonance imaging, 2-deoxy-2-fluoro [^{18}F]-D-glucose positron emission tomography/CT. The reported sensitivity and specificity, respectively, of these imaging methods are as follows: ultrasonography, 48.4%−87.1% and 55.6%−97.3%[12]; CT, 46% and 89%[13]; multidetector-row CT, 76.9% and 96.6%[14]; magnetic resonance imaging, 90% and 82%[15]; and 2-deoxy-2-fluoro [^{18}F]-D-glucose positron emission tomography/CT, 58% and 92%[13]. Because each modality has a characteristic sensitivity and specificity, satisfactory results for the diagnosis of N0 breast could not be obtained with only a single modality. Thus, multiple imaging methods should used to establish a clinical diagnosis of axillary lymph node metastasis. Ultrasound-guided fine-needle aspiration cytologic examination or core-needle biopsy of ultrasonographically suspicious nodes somewhat increases specificity[12].

In the present study, the provisional false-negative rate of SNB was calculated with data from all 65 patients with axillary metastasis. The rate of axillary recurrence was extremely low, 0.4%, which suggests that the provisional false-negative rate is valid.

Our dual-agent SNB procedure yielded a satisfactory SLN identification rate of 99.2%, a provisional false-negative rate of 7.7%, and an axillary recurrence rate of 0.4%, which were not inferior to the results of previous large-scale clinical trials[3,16,17]. Thus, we conclude that our SNB procedure is feasible.

Our series included 2 male patients and 5 cases of multifocal carcinoma, 4 of which were diagnosed after excisional biopsy. The favorable results suggest that SNB is indicated for such cases.

The classified data regarding SLN types suggests that there would have been 7 additional false-negative cases if the dye method alone had been used; however, no additional false negatives would have resulted from using the radiotracer alone.

Compared with GP, LS was less sensitive, but we consider it a useful technique because it allowed the simultaneous detection of SLNs over a wider area, including the parasternal area, and because it may exceed GP for the detection of parasternal SLNs[18].

Reported factors that influence the SLN identification rate and the accuracy of SLN status include patient age, tumor site, history of excisional tumor biopsy, tumor size, and clinical status of axillary nodes[19]. In the present study, identification of SLNs was unsuccessful in 2 patients. One patient had a high BMI, which is related to atrophy of the lymph vessels and may thus explain the failure in SLN identification. The failure in the other patient might have been caused by a sequential or regional mismatch due to the injection site of the tracer[20].

The problem of micrometastasis to SLNs remains unresolved. To improve the intraoperative detection rate of micrometastasis, the addition to the SNB protocol of such methods as 1-step nucleic acid amplification (OSNA) assay[21], which detects gene expression of cytokeratin 19, should be considered.

Disease recurrence was detected in the axilla in 1 case, which was likely a false negative. It is possible that axillary recurrence could have been prevented if postoperative therapy had been administered after the first operation.

Tracers commonly used for SNB in Japan are ^{99m}Tc-thin colloid, ^{99m}Tc-stannous phytate, indocyanine green, and indigo carmine, which were approved for reimbursement under the health insurance system in Japan in autumn 2009, based on the results of a Japanese trial performed at multiple centers, including our institution[10]. On April 1, 2010, SNB was approved for reimbursement under the health insurance system.

Controversy about SNB remains regarding indications, choice of tracer, injection site, method of pathological diagnosis, the handling of micrometastasis and isolated tumor cells, and problems related to parasternal lymph nodes. We anticipate that some of these issues will be clarified with the results of several ongoing large-scale

randomized control trials on SNB in Europe and the United States[25,22–25]. If its efficacy and safety are confirmed in these trials or subsequent meta-analyses, SNB will become a standard technique in the management of clinically node-negative breast cancer.

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