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Follow-up Results of Sentinel Lymph Node Biopsy using the Dye-Only Method for Breast Cancer

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To demonstrate the validity of sentinel lymph node biopsy (SLNB) using the indocyanine green dye method (dye only method), we compared the survival of breast cancer patients negative to SLNB without axillary lymph node dissection (ALND) (SLNB group) to that of lymph node-negative patients undergoing ALND (ALND group). We studied a total of 174 patients with T1-2N0 invasive breast cancer diagnosed at our university hospital clinical department between 2000 and 2008, with follow-up till 31 December 2009, retrospectively. The SLNB group consisted of 108 SLNB-negative women without additional ALND (median follow-up, 25 months), diagnosed between May 2005 and 2008. The ALND group consisted of 66 axillary lymph node-negative women (median follow-up, 75 months) treated with ALND between 2000 and April 2005. SLNB was performed during operation by periareolar injection using indocyanine green. All sentinel lymph nodes were examined using the largest section along the major axis, and permanent sections were stained with hematoxylin and eosin. In the SLNB group, no patients developed axillary recurrence during the 25-month median follow-up. The 4.5-year distant disease free survival and overall survival rates were 90.9% and 91.9%, respectively. The survival rate in the SLNB group was equivalent to that in the ALND group. This suggests that SLNB with the dye only method can safely replace ALND as the procedure of choice for axillary staging in breast cancer patients with a clinically negative axilla.

Key words: breast cancer; sentinel lymph node biopsy

Axillary lymph node status is one of the most important prognostic indicators for relapse and survival in patients with breast cancer (Fisher et al., 1970). Until the introduction of sentinel lymph node (SLN) mapping in the early 1990s, axillary lymph node dissection (ALND) had been the standard surgical treatment for the axilla of breast cancer patients. However, ALND is associated with major problems, including acute and chronic complications (Petrek et al., 2000).

The widespread use of screening mammography often enables detection of breast cancer at an early stage and thus, the percentage of node-positive patients who benefit from routine ALND is decreasing (Bass et al., 1999). Consequently, SLN biopsy (SLNB) has now become the new standard of care for axillary staging in early breast cancer, and it has the potential to reduce the morbidity of the surgical procedure (Veronesi et al., 2003; Fleissig et al., 2006; Lucci et al., 2007). The SLN identification rate has been reported to be 96% and SLNB sensitivity to be 93% in average (Kim et al., 2006). Many published trials have reported false-negative rates of 5 to 10%, results which were

Abbreviations: ALND, axillary lymph node dissection; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

deemed acceptable for avoiding ALND in patients with a negative sentinel node (Liberman, 2000; Veronesi et al., 2003; Krag et al., 2007).

While these initial studies are promising, follow-up data have been limited, especially for SLNB using the indocyanine green dye method (dye only method). The aim of this study was to demonstrate the accuracy of SLNB using the dye only method without ALND, as an effective tool for axillary staging. The survival of breast cancer patients negative to SLNB without ALND was compared to that of axillary lymph node-negative patients after ALND.

Subjects and Methods

Patients

A total of 174 patients with initial primary invasive breast carcinomas were treated in our Clinical Department of University Hospital between January 2000 and December 2008. We divided them into 2 groups of 108 SLNB-negative patients without ALND who were treated between May 2005 and December 2008 (SLNB group) and 66 axillary node-negative patients with ALND who were treated between January 2000 and April 2005 (ALND group). All patients had clinically negative axillas. Patients with in situ carcinomas, multicentric carcinomas, bilateral breast carcinomas, locally advanced disease with primary tumors greater than 4 cm, clinically or pathologically positive axillary lymph nodes, or who underwent systemic primary therapy, were excluded from the study. Informed consent was obtained from every patient. All patients were treated with breast-conserving surgery or mastectomy. Most patients with breast-conserving surgery received radiotherapy to the whole breast after surgery. Most patients also underwent some type of systemic adjuvant therapy.

SLNB and pathological analysis

SLNB was performed using the dye only method with 25 mg indocyanine green (Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan), which was diluted in 5 mL sterile, distilled water. After induction of general anesthesia, 3- to 5-mL indocyanine green was injected intradermally into the periareolar area. A 3- to 4-cm axillary skin incision was made 5 or 10 min after the injection, in order to detect green-stained SLNs. Intraoperative frozen-section analyses of the resected SLNs were performed. All SLNs were bisected along the major axis, and postoperatively, specimens were fixed, embedded in paraffin, and stained using standard histopathological procedures. Patients with SLNs that were negative for malignancy by intraoperative analysis did not undergo additional ALND.

Statistical analysis

The disease free survival period was defined as the period from the date of operation to the date of the first confirmation of recurrence (i.e., local recurrence or metastasis) or death from any cause, whichever came first. The overall survival period was defined as that from the date of operation to the date of death from any cause. The Mann-Whitney U test or unpaired t-test was used for comparisons of continuous outcomes, while the χ^2 test was used for comparisons of categorical variables. The disease free and overall survival curves were analyzed by the log-rank test. A Cox proportional-hazards model was used to compare the SLNB and ALND groups, and to adjust for variables. Significance was defined as $P < 0.05$.

Results

SLNB

SLNs were identified in 130 of the 135 patients (SLN identification rate, 96.3%). SLNs stained in frozen sections were negative in 108 of the 130 patients (83.1%). Three of the 108 patients (2.8%) were positive to SLNB of permanent sections stained in hematoxylin and eosin (Fig. 1). The mean number of SLNs per patient was 1.27 (range, 1–3). Thus, we determined 108 patients to be SLNB-negative in frozen sections, and treated them as the SLNB group (Fig. 1).

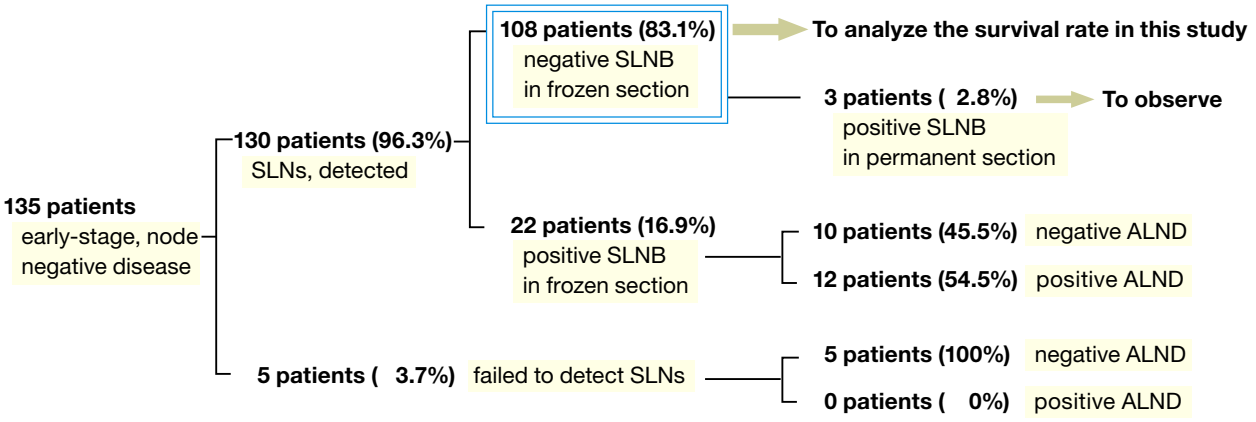


Fig. 1. Qualification of patients of the SLNB group. We analyzed the survival of 108 patients observed to be negative to SLNB intraoperatively in frozen section and successively in permanent section. ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Survival data

Patient and tumor characteristics of the SLNB and ALND groups are listed in Table 1. With the exception of tumor size (unpaired *t*-test) and follow-up period, differences were not significant in age, tumor histology, tumor laterality, estrogen receptor status, progesterone receptor status, HER-2 status, menopausal status, tumor treatment and systemic therapy.

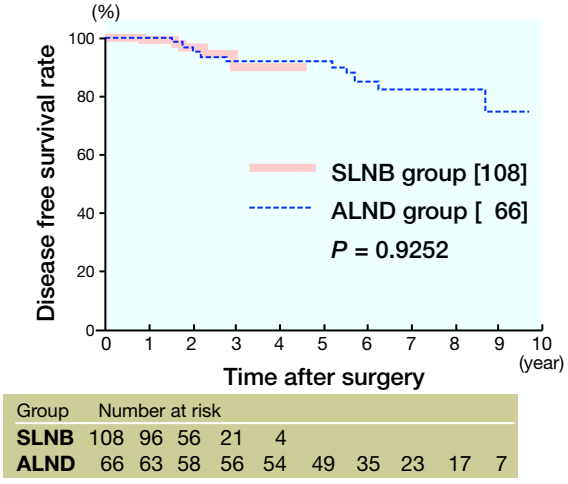
In the SLNB group, the median follow-up period was 25 months (range, 0–55 months). There

Table 1. Patient and tumor characteristics

		SLNB group [108]	ALND group [66]	*P* value
Age	Median (min–max) (year)	60 (27–86)	54 (30–87)	0.2163
Histology	Invasive ductal carcinoma	94	58	1.0000
	Others	14	8	
Tumor size	Mean (min–max) (cm)	1.6 (0.5–3)	1.9 (0.5–3.5)	0.0022*
Tumor laterality	Right	49	35	0.2625
	Left	59	31	
Estrogen receptor status	Positive	88	45	0.0509
	Negative	20	21	
Progesteron receptor status	Positive	66	38	0.7734
	Negative	42	28	
HER-2 status	Positive	9	6	0.3757
	Negative	94	37	
	Missing	5	23	
Menopausal status	Before	27	25	0.0673
	After	81	41	
Tumor treatment	Breast conserving surgery ± radiation therapy	84	53	0.8624
	Mastectomy	24	13	
Systemic therapy	None	12	7	0.2185
	Endocrine therapy	82	43	
	Chemotherapy	9	11	
	Endocrine therapy + chemotherapy	5	5	

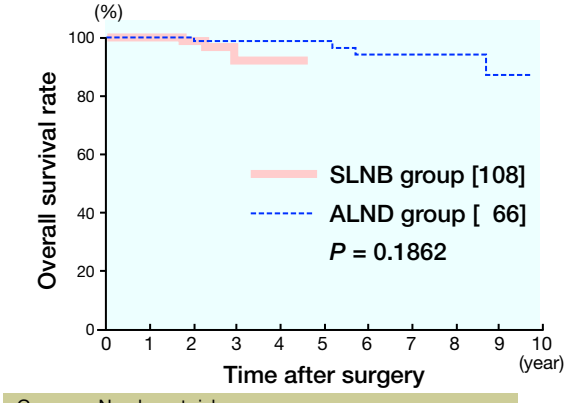
ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.
[ ], number of patients.
* $P < 0.05$ with unpaired *t*-test.

were no axillary recurrences in the 108 patients who underwent SLNB without ALND. A metastasis to the bone was observed in 1 patient. Three patients died of other causes. The disease free and overall survival rates at 4.5 years were 90.9% and 91.9%, respectively (Figs. 2 and 3).



Group	Number at risk									
SLNB	108	96	56	21	4					
ALND	66	63	58	56	54	49	35	23	17	7

Fig. 2. Changes in disease free survival rate in the SLNB and ALND groups. The difference in prognostic significance of the disease free survival rate between groups was $P = 0.9252$. ALND, axillary lymph node dissection; SLNB, senile lymph node biopsy. [ ], number of patients.



Group	Number at risk									
SLNB	108	97	57	21	4					
ALND	66	63	60	59	58	52	37	27	20	9

Fig. 3. Changes in overall survival rate in the SLNB and ALND groups. The difference in prognostic significance of the overall survival rate between groups was $P = 0.1862$. ALND, axillary lymph node dissection; SLNB, senile lymph node biopsy. [ ], number of patients.

In the ALND group, the median follow-up period was 75 months (range, 0–116 months). There were no axillary recurrences in the 66 patients who underwent ALND. Contralateral breast cancer was observed in 3 patients, ipsilateral recurrence in 1 patient and cervical lymph node metastasis in 1 patient. Three patients died of other causes. The disease free and overall survival rates at 4.5 years were 91.7% and 98.3%, respectively (Figs. 2 and 3). After adjusting for tumor size in Cox proportional-hazards model analysis, tumor size was not a significant predictor for both survival rates.

Discussion

In this study, we determined the disease free and overall survival rates in patients undergoing SLNB without ALND, and compared with those in node-negative patients undergoing ALND. Although several studies have validated the accuracy of SLNB for axillary staging (Krag et al., 1998; Lo et al., 2006; Gill, 2009), the data on the long-term outcome of SLNB without ALND have been limited.

The 4.5-year overall and disease free survival rates we observed in the SLNB group were 90.9% and 91.9%, respectively. Other studies have reported that for early-stage breast cancer, the 5-year overall survival rate was 89 to 96.7% in the SLNB group, and 85 to 88.5% in the ALND group (Kuijt et al., 2003; Langer et al., 2009), and that the 5-year disease free survival rate was 87.6 to 96.0% in the SLNB group and 87.2 to 89.9% in the ALND group (Zavagno et al., 2008; Langer et al., 2009). These suggest that SLNB without ALND provides at least equivalent or improved disease free and overall survival rates compared with ALND for node-negative patients. This is most likely because of more accurate staging resulting from the focused pathologic examination on 1 or just a few nodes. Prospective randomized comparisons of SLNB with routine ALND are now ongoing in the American National Surgical Adjuvant Breast and Bowel Project Protocol-B 32 and the European ALMANAC trials.

In our study with a median follow-up period of 25 months, there were no axillary recurrences in the SLNB group. All of our patients were negative to SLNB with the dye only method, which was successively defined in hematoxylin and eosin staining only of the largest single section of the SLN, and so isolated tumor cells or a micrometastasis may have been overlooked. We calculated the mean rate of axillary recurrence in SLNB-negative patients to be 0.51% from results of 8 different studies with a mean follow-up period of 34.9 months (Salem, 2009). Thus far in the current literature, research has not provided evidence that SLN micrometastasis leads to axillary recurrence or distant disease, which supports the theory that formal ALND may be omitted in these patients (Langer et al., 2005). In patients with isolated tumor cells or micrometastasis who received adjuvant therapy, disease-free survival was improved (de Boer et al., 2009). These results suggest that adjuvant treatment contributes to the low axillary failure rate, and that good disease free survival may have resulted in good overall survival in our SLNB group, because 90% of the patients in our study received systemic adjuvant therapy. Another reason for our results may be the short follow-up period, but a median time interval of 19 months for local recurrence after ALND has been reported in another study (Newman et al., 2000).

We used indocyanine green dye at SLNB. Indocyanine green dye has been commonly used in clinical practice and the safety has been established when SLNB was introduced. Furthermore, the side effect associated with allergy has been concerned about other dyes. Nationwide questionnaire survey on SLNB reported no side effects for indocyanine green dye (Tsugawa et al., 2009).

The main limitation of the present study is that patient groups studied in 2 different periods of time were compared. However, follow-up procedures and adjuvant treatments were similar for both groups, because all patients had early-stage, node-negative disease. Second, although most patient and tumor characteristics were similar in both groups, there were significantly more patients with larger tumor size in the ALND group than in the SLNB group. However, tumor size was not a significant predictor for the disease free and overall survival rates after adjusting for the factor in Cox proportional-hazards model analysis.

In conclusion, survival in node-negative breast cancer patients undergoing SLNB with the dye only method without ALND was equivalent to that in node-negative breast cancer patients undergoing ALND. This suggests that SLNB with the dye only method can safely replace ALND as the procedure of choice for axillary staging in breast cancer patients with a clinically negative axilla.

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