

Clinical outcomes after sentinel lymph node biopsy in clinically node-negative breast cancer patients

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Purpose: To evaluate non-sentinel lymph node (LN) status after sentinel lymph node biopsy (SNB) in patients with breast cancer and to identify the predictive factors for disease failure.

Materials and Methods: From January 2006 to December 2007, axillary lymph node (ALN) dissection after SNB was performed for patients with primary invasive breast cancer who had no clinical evidence of LN metastasis. A total of 320 patients were treated with breast-conserving surgery and radiotherapy.

Results: The median age of patients was 48 years, and the median follow-up time was 72.8 months. Close resection margin (RM) was observed in 13 patients. The median number of dissected SNB was two, and that of total retrieved ALNs was 11. Sentinel node accuracy was 94.7%, and the overall false negative rate (FNR) was 5.3%. Eleven patients experienced treatment failure. Local recurrence, regional LN recurrence, and distant metastasis were identified in 0.9%, 1.9%, and 2.8% of these patients, respectively. Sentinel LN status were not associated with locoregional recurrence ($p > 0.05$). Close RM was the only significant factor for disease-free survival (DFS) in univariate and multivariate analysis. The 5-year overall survival, DFS, and locoregional DFS were 100%, 96.8%, and 98.1%, respectively.

Conclusion: In this study, SNB was performed with high accuracy and low FNR and high locoregional control was achieved.

Keywords: Breast neoplasms, Sentinel lymph node biopsy, Axillary lymph node dissection, Neoplasm recurrence, Local

Introduction

In invasive breast cancer, axillary lymph nodal status is considered to be an important prognostic factor for predicting clinical outcome. Since the 1990s, sentinel lymph node biopsy (SNB) has been performed routinely for evaluating axillary lymph node (ALN) status and reducing complications of axillary lymph node dissection (ALND). In several studies,

SNB could accurately predict ALN status in clinically node-negative breast cancer patients. Only 5%–15% of early breast cancer patients with negative sentinel lymph node (SLN) had additional ALN metastasis [1-3]. Because ALND increases the risk of complications, such as lymphedema, chronic shoulder pain, arm weakness and joint dysfunction without survival benefit, completion ALND is not routinely performed in SLN-negative patients [2,4,5].

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In patients with positive SLN, additional ALN involvement is observed in 40%–60%. Because additional ALN metastasis is considered to be a significant risk factor for disease progression, completion ALND is recommended for regional control in SLN-positive patients [6]. However, several prospective trials have shown that the regional failure rate is lower than expected in patients without ALND who received SNB only based on the incidence of axillary metastases. No survival difference was observed between patients with SNB only and patients with SNB and completion ALND or regional radiotherapy [7–10]. Based on the result of these clinical trials, additional ALND may be minimized in clinically node-negative patients with T1 and T2. The purpose of this study was to investigate the association between SLN status and ALN status in clinically node-negative early breast cancer patients and to evaluate the clinical outcomes after SNB and ALND in our institution.

Materials and Methods

We retrospectively performed a chart review of primary breast cancer patients treated with whole breast radiotherapy at our hospital, between January 2006 and December 2007. The criteria for entry into this study were as follows: 1) pathologically proven invasive breast cancer, 2) no clinical evidence of lymph node metastasis, 3) performance of breast-conserving surgery, SNB, and ALND, and 4) completion of whole breast radiotherapy with or without regional node irradiation. We excluded patients who were male; had a history of breast irradiation, stage IV or recurrent breast cancer and who underwent neoadjuvant chemotherapy. A total of 320 patients were eligible.

For staging work-up, all patients received mammography, ultrasound of breast, abdomen and whole body bone scan. In some patients, breast magnetic resonance imaging was done for work-up. We defined clinically node-negative (cN0) as a no evidence of lymph node metastasis in the preoperative imaging study and physical examination. Two patients with palpable ALN or typical metastatic lymph node (round shape, obliterated hilum) received fine needle aspiration biopsy, and the result was negative. SLN detection was only performed using the radio-isotope technique. On the day of surgery, 18.5 MBq (0.5 mCi) 99mTc-Phytate (Korea Atomic Energy Research Institute, Daejeon, Korea) diluted in 0.5 mL saline was injected at the upper outer subareolar. A lymphatic scintigram was obtained for each patient. In the operating room, a hand-held

gamma detector (Navigator GPS; RMD Inc., Watertown, MA, USA) was used to locate the SLNs. Four patients who fail SLN detection were excluded from this study.

ALND was performed for all patients following SNB. During this period, completion ALND performed even if the SLN was negative, because surgeons wanted to make sure negative ALN after negative SLN. All enrolled patients were staged according to the American Joint Committee on Cancer (AJCC) 7th staging system. A surgical margin was diagnosed as close if tumor were 2 mm or less from postsurgically applied inked margin.

All analyses were performed using SPSS software ver. 20.0

Table 1. Patient characteristics

Characteristic		No. of patients (%)
Age (yr), median (range)		48 (25–76)
AJCC stage		
IA	T1N0M0	189 (59.1)
IB	T1N1miM0	13 (4.1)
IIA	T1N1M0	43 (13.4)
	T2N0M0	43 (13.4)
IIB	T2N1M0	21 (6.6)
IIIA	T1N2M0	5 (1.6)
	T2N2M0	5 (1.5)
	T3N1M0	1 (0.3)
Estrogen receptor status		
	Positive	220 (68.8)
	Negative	99 (30.9)
	Unknown	1 (0.3)
Progesterone receptor status		
	Positive	199 (62.2)
	Negative	120 (37.5)
	Unknown	1 (0.3)
HER2		
	0, 1+, 2+	280 (87.5)
	3+	39 (12.2)
	Unknown	1 (0.3)
Histology		
	IDC	288 (90.0)
	Other	32 (10.0)
Extensive intraductal component		
	No	246 (76.9)
	Yes	51 (15.9)
	Unknown	23 (7.2)
Histologic grade		
	1	71 (22.2)
	2	143 (44.7)
	3	75 (23.4)
	Unknown	31 (9.7)

AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma.

(IBM, Armonk, NY, USA). Overall survival (OS), disease-free survival (DFS), locoregional DFS (LRDFS) were analyzed using the Kaplan-Meier method and univariate analysis of clinical factors influencing each failure were analyzed using the log-rank test. Multivariate analysis was performed using the Cox-proportional hazard model. The p-values less than 0.05 were considered statistically significant.

Results

1. Patient characteristics

Patient characteristics are shown in Table 1. The median age was 48 years (range, 25 to 76 years). According to AJCC

7th stage, the number of patients with stage IA, IB, IIA, IIB, and IIIA was 189 (59.1%), 13 (4.1%), 86 (26.9%), 21 (6.6%), and 11 (3.4%), respectively. The most common histologic type of tumor was invasive ductal carcinoma (288, 90.0%). Estrogen receptor positive, progesterone receptor positive, and c-erbB2 3+ was found in 220 patients (68.8%), 199 (62.2%), and 39 (12.2%), respectively. In c-erbB2 2+ patients by immunohistochemistry, FISH or SISH was done for 7 patients (26%). Among them, c-erbB2 amplification by FISH or SISH was observed in one patient. Extensive intraductal component was found in 51 patients (15.9%).

2. Treatment characteristics

Treatment characteristics are summarized in Table 2. The median number of removed nodes was two (range, 1 to 16), and positive SLN was found in 69 patients (21.6%). The median number of removed ALNs was 11 (range, 1 to 35), and additional involved lymph nodes were found in 38 patients (11.9%). Among the patients with negative SLN, positive conversion in permanent section was shown in two patients. Close or positive resection margin (RM) were found in 13 patients (4.1%). All patients received whole breast irradiation with median of 50.4 Gy in 28 fractions, and 313 patients (97.8%) received a tumor bed boost with a median dose of 9 Gy. Treatment included the breast only in 294 patients (91.9%), breast and supraclavicular lymph node (SCL) in 26 patients with positive axillary node (8.1%), and breast, SCL, and internal mammary lymph node in 20 patients with inner/central tumor with or without positive axillary node (6.3%).

Most patients (300, 93.6%) received systemic treatments; chemotherapy alone in 83 patients (25.9%), hormonal therapy alone in 81 patients (25.3%), and both in 133 patients (41.6%). Among the 219 patients who received chemotherapy, doxorubicin and cyclophosphamide (AC) were used in 124 patients (56.6%); doxorubicin, cyclophosphamide, and paclitaxel (ACT) in 64 patients (29.2%), and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in 17 patients (7.8%).

Table 2. Treatment characteristics

Characteristic	No. of patients (%)
No. of dissected SLNs	2 (1–16)
1	133 (41.6)
2	85 (26.6)
3	42 (13.1)
4	30 (9.4)
5	14 (4.4)
≥6	16 (5.0)
No. of metastatic SLNs	
0	251 (78.4)
1	51 (15.9)
2	11 (3.4)
3	3 (0.9)
≥4	4 (1.3)
No. of dissected ALNs	11 (1–35)
Additional involved nodes	
No	282 (88.1)
Yes	38 (11.9)
Close or positive RM	
No	307 (95.9)
Yes	13 (4.1)

Values are presented as median (range) or number (%). SLN, sentinel lymph node; ALN, axillary lymph node; RM, resection margin.

Table 3. FNR rate according to the number of dissected SLNs

No. of dissected SLNs	No. of patients	TN	FN	TP	FNR (%)	Accuracy (%)
1 or more	320	234	17	21	5.3	94.7
2 or more	187	136	9	12	4.0	96.1
3 or more	102	70	3	9	1.3	98.7
4 or more	60	40	0	7	0	100

SLN, sentinel lymph node; TN, true negative; FN, false negative; TP, true positive; FNR, false negative rate.

Two hundred fourteen patients who received hormonal therapy; tamoxifen in 157 patients (73.4%) and letrozole in 45 (21.0%).

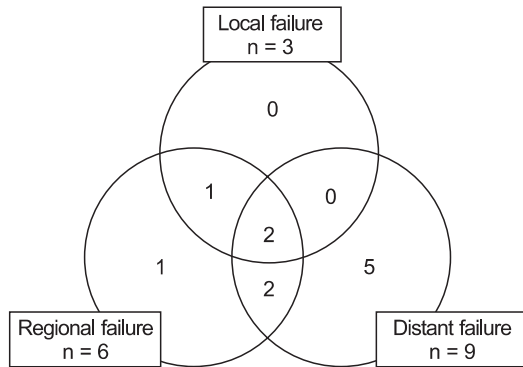


Fig. 1. Patterns of failure. Eleven patients developed treatment failure; local recurrence, regional lymph node recurrence, and distant metastasis were identified in three patients (0.9%), six (1.9%), and nine (2.8%), respectively.

3. Accuracy and false negative rate of sentinel node biopsy
 SNB and ALND were performed in all patients. Sixty-nine patients had positive sentinel node, and additional involved nodes were shown in 38 patients. Table 3 shows the accuracy and false negative rate (FNR) according to the number of dissected SLNs. The sentinel node accuracy was 94.7% and the FNR was 5.3% in all patients with ALND. The FNR of the biopsy decreased as the number of removed lymph nodes increased. Specifically, the FNR was 0% when more than four lymph nodes were removed. There were 21 true positive, 234 true negative, and 17 false negative results.

4. Survival outcomes, patterns of failure, and prognostic factors

With a median follow-up of 72.8 months (range, 6 to 91 months), 11 patients (3.4%) experienced disease progression during the follow-up period. The patterns of failure are illustrated in Fig. 1. Local recurrence, regional lymph node recurrence and distant metastasis were identified in three

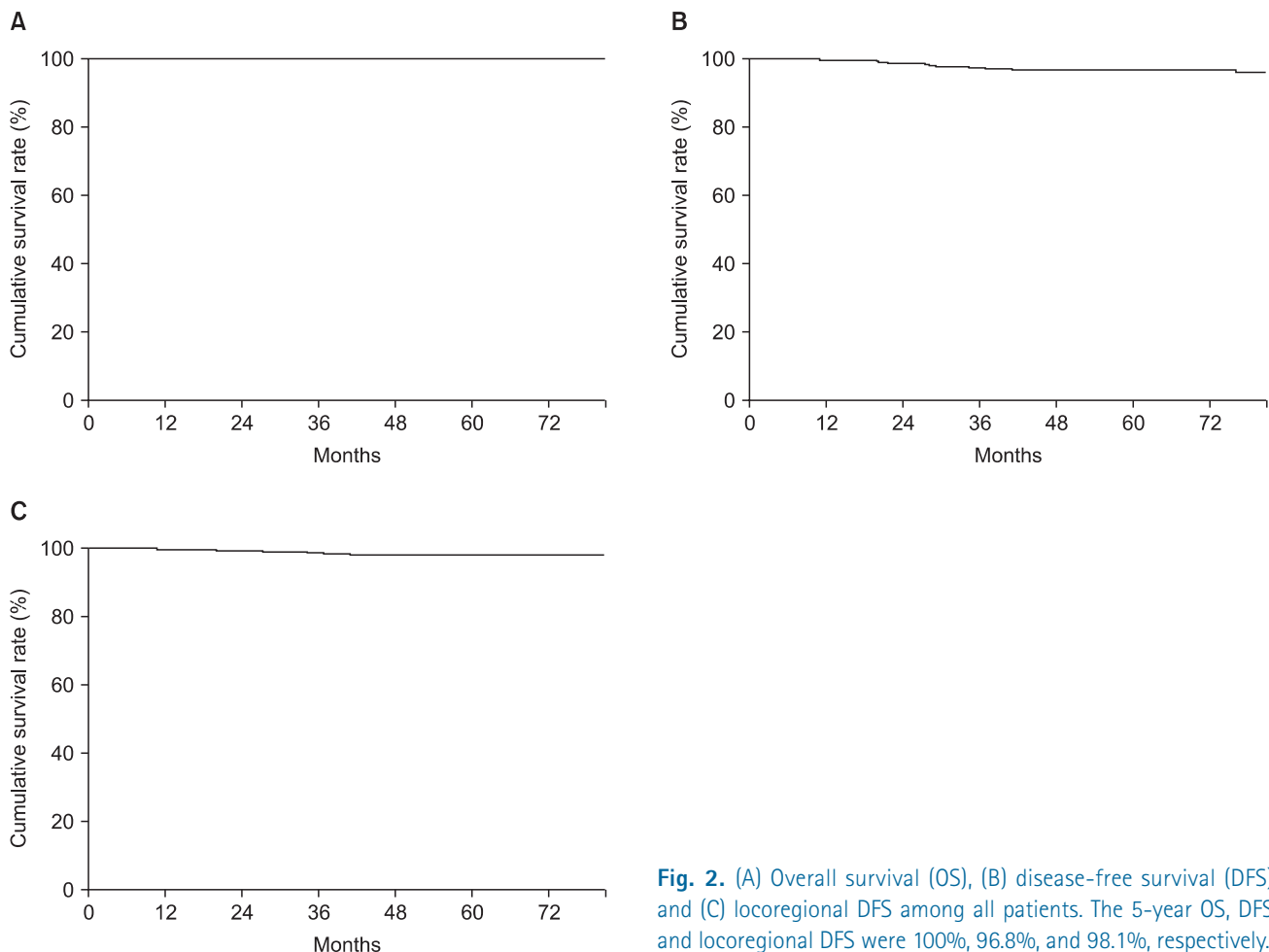


Fig. 2. (A) Overall survival (OS), (B) disease-free survival (DFS), and (C) locoregional DFS among all patients. The 5-year OS, DFS, and locoregional DFS were 100%, 96.8%, and 98.1%, respectively.

patients (0.9%), six (1.9%) and nine (2.8%), respectively. Locoregional recurrence occurred in six patients. Among them, only two patients had locoregional recurrence without distant metastasis. The 5-year OS, DFS, and LRDFS were 100%, 96.8%, and 98.1%, respectively (Fig. 2). In univariate and multivariate analyses, close RM was the only significant factor for lower DFS ($p = 0.014$) (Table 4). Neither SLN nor non-SLN status was significantly associated with locoregional recurrence and disease recurrence ($p > 0.05$).

Table 4. Univariate and multivariate associations of prognostic factors with recurrence-free survival

Variables	No. of patients	p-value	
		Univariate	Multi-variate
Age (yr)		0.463	0.221
<50	199		
>50	121		
T stage		0.879	0.648
T1	250		
T2	69		
T3	1		
SLN status		0.773	0.176
Negative	251		
Positive	69		
No. of positive LN		0.013	0.727
0	224		
1	51		
2	26		
≥ 3	19		
EIC		0.760	0.544
Yes	51		
No	246		
Close RM		0.003	0.014
Yes	13		
No	307		
Molecular subtype		0.633	0.384
Luminal A	211		
Luminal B	24		
Triple negative	18		
HER2	66		
Regional LN irradiation		0.854	0.603
Yes	26		
No	294		
Adjuvant systemic treatment		0.388	0.989
Yes	300		
No	20		

LN, lymph node; EIC, extensive intraductal component; RM, resection margin; HER2, human epidermal growth factor receptor 2.

Discussion and Conclusion

ALN status is an important prognostic factor of survival outcome and a predictor of regional and systemic recurrence in breast cancer. Therefore, complete ALND is routinely performed in breast cancer patients regardless of early or advanced disease. Generally, eight or more axillary nodes should be routinely dissected irrespective of lymph node metastasis because many surgeons consider the number of dissected ALNs to be associated with accurate evaluation of ALN status. Despite the high locoregional and systemic control rates after ALND completion, most patients experience several complications, such as lymphedema, shoulder pain, and numbness. To reduce these complications, SNB was demonstrated by Giuliano et al. [11] to be an effective and minimally invasive alternative to ALND for identifying lymph node status. Thereafter, many studies investigated the efficacy and clinical outcomes of SNB, and SNB is now widely used in early breast cancer treatment.

In early breast cancer patients with negative SLN, no further ALND is recommended. In the case of sentinel node metastasis, most clinical practice guidelines recommend complete ALND. Although additional ALN involvement was found in 35%–60% of positive SLN patients, the axillary recurrence rate is reported to be 0.2%–0.9% for micrometastatic disease of SLN and around 1% for macrometastatic disease [9,12–15]. Based on these results, the hypothesis that ALN metastatic disease does not cause regional recurrence has been accepted. Therefore, several randomized phase 3 trials have been performed to investigate whether ALND can safely be omitted in early breast cancer patients with positive SLN. In the American College of Surgeons Oncology Group Z0011 trial, clinically node-negative early breast cancer patients with positive SLN were randomized to ALND or no ALND groups. At the median follow-up of 6.3 years, no difference was observed between groups for OS, progression-free survival (PFS) or locoregional PFS. The International Breast Cancer Study Group trial 23-01 trial was designed to determine whether no ALND was inferior to ALND in patients with one or more micrometastatic SLN with a tumor of maximum 5 cm. After a median follow-up of 5 years, no difference was found between the ALND and no ALND groups for OS or PFS. In both trials, axillary recurrence in the no ALND group was about 1%. In the AMAROS trial, ALND and axillary radiotherapy were compared. After a follow-up of 5 years, axillary radiotherapy was equivalent to ALND in OS, PFS, and axillary recurrence [7,9,16].

In the present study, our institutional practice achieved a high locoregional control rate through SNB and ALND. The accuracy and FNR of SNB are comparable to previously published studies [17,18]. Currently, ALND is not routinely performed in patients with negative SLN. Many surgeons insist that ALND should be carried out routinely in positive SLN patients because additional ALN involvement has been found in 35%–60% of patients. But axillary recurrence rate in patients with positive SLN was lower than expected in previous studies, even if patient underwent breast-conserving surgery without ALND.

In our institution, SNB was performed with high accuracy and low FNR. Sentinel node status was not associated with axillary recurrence. High locoregional control was achieved with SNB and ALND. Based on these results, axillary dissection might be individualized in early breast cancer patients according to sentinel node metastasis.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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