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ORIGINAL ARTICLE

Sentinel Lymph Node Biopsy Alone after Neoadjuvant Chemotherapy in Patients with Initial Cytology-Proven Axillary Node Metastasis

Ji Young Kim*, Min Kuk Kim[1], Jeong Eon Lee[2,*], Yongsik Jung, Soo Youn Bae[2], Se Kyung Lee[2], Won Ho Kil[2], Seok Won Kim[2], Ku Sang Kim[3], Seok Jin Nam[2], Sehwan Han

Department of Surgery, Ajou University School of Medicine, Suwon; [1]MD Hospital, Seoul; [2]Department of Surgery, Sungkyunkwan University School of Medicine, Seoul; [3]Ulsan City Hospital, Ulsan, Korea

Purpose: Neoadjuvant chemotherapy (NAC) has been recently used to downstage breast cancer. However, in patients with initial axillary lymph node (ALN) metastasis, ALN dissection regardless of the NAC response remains the standard treatment. The purpose of this study was to identify the feasibility and accuracy of sentinel lymph node biopsy (SLNB) after NAC in patients with ALN metastasis at diagnosis. **Methods:** From January 2007 to August 2013, data of patients who were diagnosed with invasive breast cancer and ALN metastasis and treated with NAC followed by definitive surgery in two centers were collected retrospectively. A total of 386 patients were enrolled and classified into five groups according to surgical procedure for the ALNs and pathologic results. **Results:** At SLNB after NAC, sentinel lymph nodes (SLNs) that stained blue or were hot, including suspicious nodes, were identified; the SLN identification and false-negative rates was 96% and 10%, respectively. There was no difference in the overall survival among the groups. For patients who revealed a pathologic complete node response, there was a significant difference in the disease-free survival rate between the SLNB only and complete ALN dissection groups ($p=0.031$). However, the rate of axillary recurrence demonstrated no significant differences among the groups ($p>0.050$) **Conclusion:** SLNB after NAC in breast cancer patients with initial ALN metastasis may help identify downstaging to negative nodal status and thereby reduce the surgical morbidity by avoiding standard ALN dissection.

Key Words: *Axilla, Breast neoplasms, Neoadjuvant therapy, Neoplasm metastasis, Sentinel lymph node biopsy*

INTRODUCTION

Accurate staging and proper management of axillary lymph nodes (ALNs) are important for the treatment of breast cancer. Nodal staging is successfully achieved by sentinel lymph node biopsy (SLNB) in clinically node-negative patients [1]. Neoadjuvant chemotherapy (NAC), was initially used to convert inoperable locally advanced breast cancer to operable status, and has been recently used to downsize tumors to allow for breast conservation surgery [2,3]. Moreover, NAC has been shown to effectively downstage the ALNs [4-6]. However, a complete ALN dissection (ALND), regardless of the NAC response, remains the standard management for all patients with a cytology-proven ALN metastasis at diagnosis [7].

NAC offers the advantages of real-time monitoring and confirmation of the treatment effects in terms of the pathological complete response (pCR) [8,9]. Several trials have shown that the achievement of a pCR after chemotherapy strongly correlates with favorable long-term outcomes among the different breast cancer subtypes [10,11]. Of note, the triple-negative and human epidermal growth factor receptor 2 (HER2) subtypes are more likely to obtain pCR when NAC is administered, as compared to the luminal A subtype [12,13].

The rate of conversion to negative ALN after NAC ranges from 30% to 40%. These patients would not be expected to benefit from ALND and may experience complications from the procedure. ALN pCR is associated with an excellent prognosis despite an excess of aggressive features [14,15]. Furthermore, growing evidence suggests that the nodal stage after NAC reflects the prognosis more accurately than the initial axillary status [16]. As a result, questions are arising whether removal of the lymph nodes with ALND is indeed needed for

Correspondence to: **Yongsik Jung**
Department of Surgery, Ajou University School of Medicine, 206 World cup-ro, Yeongtong-gu, Suwon 443-721, Korea
Tel: +82-31-219-5200, Fax: +82-31-219-5755
E-mail: smartblade@gmail.com

*These authors equally contributed to this work.

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such patients.

The objectives of this study were to evaluate the feasibility and accuracy of SLNB, to assess the patient selection factors associated with SLNB alone and to determine whether SLNB alone versus SLNB with ALND is associated with differences in the axillary recurrence or in the survival of breast cancer patients with initial cytology-proven axillary node metastasis after NAC.

METHODS

This was a retrospective two-center study conducted at the Samsung Medical Center and the Ajou Medical Center. Data of patients with a diagnosis of invasive breast cancer and axillary node-positive disease identified by ultrasound-guided fine-needle aspiration (FNA) and treated with NAC followed by definitive surgery between January 2007 and August 2013 were collected and reviewed. Clinical and pathologic characteristics were analyzed at diagnosis, after chemotherapy and after surgery. Patients with bilateral breast cancer, previous ipsilateral axillary surgery, inflammatory breast cancer or distant metastasis were excluded. The NAC regimens were decided at the discretion of the treating oncologists. Ultrasound of the regional lymph nodes and breast magnetic resonance imaging (MRI) were performed before and after NAC. The nodal size, morphology, and clinical response were assessed by ultrasound and MRI. Both, radioactive colloid and blue dye were used for sentinel lymph node (SLN) detection. Non-blue or non-hot nodes with suspicious features for metastases, and enlarged or hard nodes on palpation, were also harvested. Blue or hot nodes as well as suspicious lymph nodes, were defined as sentinel nodes. Preoperative lymphatic mapping and SLNB were performed along with, or without, completion ALND. Most patients subsequently received completion ALND after SLNB, regardless of the SLN status, following the general recommendations at the time of surgery. In cases where the patients had converted to clinically negative axillary status after chemotherapy and had confirmed negative SLN status on pathology, further ALND was omitted when the physician and patient made a decision before surgery to avoid possible morbidities from ALND.

This study was approved by the Institutional Review Boards of the Samsung Medical Center and Ajou Medical Center (approval numbers: SMC 2013-10-128 and AMC 2013-13-474).

Patient grouping

A total of 386 patients with a diagnosis of invasive breast cancer and metastatic axillary nodes documented by ultrasound-guided FNA treated with NAC followed by surgery were identified. Of these, 266 patients (68.9%) underwent complete ALND regardless of the axillary clinical response assessment after chemotherapy, after a general recommendation. SLNB was attempted for axillary staging at the time of surgical treatment in 120 patients (31.1%) with a complete or near complete clinical response on axillary ultrasound and MRI after NAC. We classified the patients into five categories: group 1, patients for whom SLNB revealed no residual axillary metastasis and no further dissection was performed; group 2, patients with negative SLN status undergoing further ALND; group 3, patients with positive or undetected SLNs undergoing further ALND; group 4, patients without residual axillary metastasis on pathology undergoing complete ALND regardless of the clinical response; and group 5, patients with pathologic nodal positive disease undergoing ALND (Figure 1). We analyzed and compared the outcomes, including the prognoses and survivals, between all groups.

During the patient grouping, we had some difficulties owing to the inherent biases of a retrospective design in distinguishing between groups 1 and 2, because some of the patients had conglomerated SLNs after chemotherapy or there were, a small number of retrieved lymph nodes even after axillary dissection. Thus, we created the following criteria for dividing the groups: the number of retrieved sentinel nodes was limited to seven for distinguishing SLNB from ALND, and the surgeon's intention of SLNB or axillary dissection was considered in addition to the number of dissected axillary nodes.

Statistical analysis

The chi-square test and Spearman correlation coefficient were used to compare discrete variables. Survival analysis was

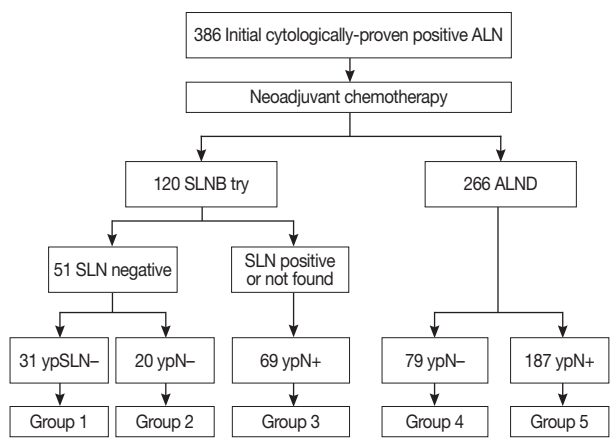

Figure 1. Summary of patient selection and grouping of patients with initial cytology-proven nodal disease at presentation.
ALN = axillary lymph node; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; SLN = sentinel lymph node.

performed using the Kaplan-Meir method and the *p*-value was calculated by using the log-rank test. A $p < 0.05$ indicated statistical significance. SPSS version 18.0 (SPSS Inc., Chicago, USA) was used for all statistical analyses.

RESULTS

Patient and tumor characteristics

The patient and tumor characteristics are summarized according to the different groups in Table 1. When we compared the patient demographics and other variables, including breast pathology after surgery, the patients in the sentinel node negative groups had significantly higher rates of ypT0 or ypTis. Furthermore, there were more patients with hormone receptor negative tumors in groups 1 and 2 than in the sentinel node negative groups.

Diagnostic performance of SLNB

The diagnostic performances of SLNB after NAC in node-positive breast cancer are demonstrated in Table 2. SLN identification was successful in 115 patients (95.8%). The median number of retrieved SLNs was 3.0 (range, 1–7). The rate of no residual axillary metastases and false-negative ratio were calculated with data of 89 patients (groups 2 and 3). The SLNB after NAC accurately predicted the nodal positivity in 18 of 20 patients (90.0%), yielding a false-negative rate of 10.0%. The diagnostic performances according to the number of SLNs examined in all patients who underwent SLNB and further ALND are demonstrated in Table 3. Although SLNB with less

Table 2. Diagnostic performance of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with initial cytology-proven nodal disease at presentation

Findings of SLN	No. (%)
SLN identification rate after NAC	115/120 (95.8)
No. of nodes retrieved*	3 (1–7)
No residual axillary metastases (ypN0)	18/89 (20.2)
Residual axillary metastases	71/89 (79.8)
Residual metastases limited to SLNs	27/70 (38.6)
Falsely negative SLNs	2/20 (10.0)

SLN = sentinel lymph node; NAC = neoadjuvant chemotherapy.
*Median (range).

Table 1. Characteristics of sentinel lymph node biopsy group and pathological node negative axillary lymph node dissection group

Variable	Total (n = 199) No. (%)	Group 1 (n = 31) No. (%)	Group 2 (n = 20) No. (%)	Group 3 (n = 69) No. (%)	Group 4 (n = 79) No. (%)	*p*-value
Age at diagnosis (yr)*	45.6 ± 9.3	47.6 ± 8.1	46.3 ± 10.8	43.3 ± 9.2	47.2 ± 10.3	0.681
Menopausal						0.279
Premenopausal	129 (64.8)	20 (64.5)	14 (70.0)	50 (72.5)	45 (57.0)	
Postmenopausal	70 (35.2)	11 (35.5)	6 (30.0)	19 (27.5)	34 (43.0)	
Histologic type						0.598
Ductal	195 (98.0)	31 (100.0)	20 (100.0)	68 (98.6)	76 (96.2)	
Lobular or others	4 (2.0)	0	0	1 (1.4)	3 (3.8)	
Hormone receptor status						< 0.001
Positive	96 (48.2)	11 (35.5)	8 (40.0)	42 (60.9)	35 (44.3)	
Negative	103 (51.7)	20 (64.5)	12 (60.0)	27 (39.1)	44 (55.7)	
HER2 status						0.007
Positive	75 (37.7)	14 (45.2)	11 (55.0)	15 (21.7)	35 (44.3)	
Negative	124 (62.3)	17 (54.8)	9 (45.0)	54 (78.3)	44 (55.7)	
Type of surgery						0.309
Conserving	147 (73.8)	28 (90.3)	15 (75.0)	51 (73.9)	53 (67.1)	
Mastectomy	52 (26.1)	3 (9.7)	5 (25.0)	18 (26.1)	26 (32.9)	
Pathologic tumor stage						< 0.001
ypT0-is	84 (42.2)	21 (67.7)	13 (65.0)	11 (15.9)	39 (49.4)	
ypT1-2	96 (48.2)	10 (32.3)	7 (35.0)	46 (66.7)	33 (41.8)	
ypT3	19 (9.5)	0	0	12 (17.4)	7 (8.9)	
Histologic grade						< 0.001
I/II	94 (47.2)	7 (22.6)	5 (25.0)	54 (78.3)	28 (35.4)	
III	36 (18.1)	6 (19.4)	3 (15.0)	10 (14.5)	17 (21.5)	
Lymphovascular invasion						< 0.001
Absent	107 (53.8)	15 (48.4)	8 (40.0)	38 (55.1)	46 (58.2)	
Present	45 (22.6)	4 (12.9)	3 (15.0)	27 (39.1)	11 (13.9)	

HER2 = human epidermal growth factor receptor 2.
*Mean ± SD.

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than three retrieved SLNs was performed in more than half of the patients (60.0%), there were no false negative SLNB findings in those patients.

Survivals

The median follow-up time was 19.5 months (range, 2–65 months). There was no difference in the overall survival among groups 1, 2, and 4 (Figure 2A), and no patient expired in all groups except for in group 5. The comparison of disease-free survival in groups 1 and 2 showed no statistical significant difference ($p=0.314$). On the other hand, there was a significant difference in the disease-free survival rate between groups 1 and 4 (77.1% vs. 85.4%). The patients treated with complete ALND and showing a pathologic complete node response had a significantly better disease-free survival compared to group 1 ($p=0.031$) (Figure 2B).

During the study period, five of the 31 patients (16.1%) in the group 1 experienced two systemic and three regional recurrences. Table 4 summarizes the types of recurrences and clinical characteristics in this group. Further, in the SLNB

Table 3. Diagnostic performance of sentinel lymph node biopsy after neoadjuvant chemotherapy according to the number of retrieved sentinel lymph nodes

No. of retrieved SLNs	No. of cases (n=89)	Status of SLNB, No. (%)		
		True positive	True negative	False negative
1	19	12 (63.2)	7 (100.0)	0
2	16	11 (68.8)	5 (100.0)	0
3	21	19 (90.5)	1 (50.0)	1 (50.0)
≥4	28	22 (78.6)	5 (83.3)	1 (16.6)
Not found	5	-	-	-

SLN=sentinel lymph node; SLNB=sentinel lymph node biopsy.

Table 4. Type of recurrence in patients with sentinel lymph node biopsy only group after neoadjuvant chemotherapy in cytology-proven node positive disease

Case	Recurrence	DFS time (mo)	HR status	HER2 status	Breast pCR	No. of retrieved SLNs
1	Brain	5	Negative	Positive	Yes	3
2	Brain	6	Positive	Positive	No	3
3	SCN	6	Positive	Negative	Yes	4
4	SCN	7	Negative	Negative	No	5
5	Axillary	10	Negative	Negative	No	2

DFS=disease-free survival; HR=hormone receptor; HER2=human epidermal growth factor receptor 2; pCR=pathological complete remission; SLN=sentinel lymph node; SCN=supraclavicular node.

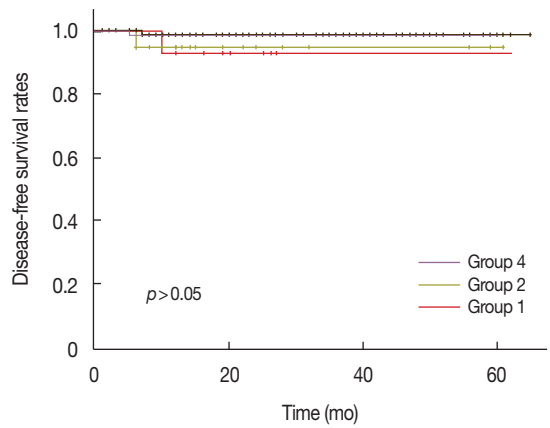

Figure 3. Kaplan-Meier survival curves for axillary event-free survival in groups 1, 2, and 4 (3.3%, 5.0%, and 1.3%, log-rank test, $p>0.05$).

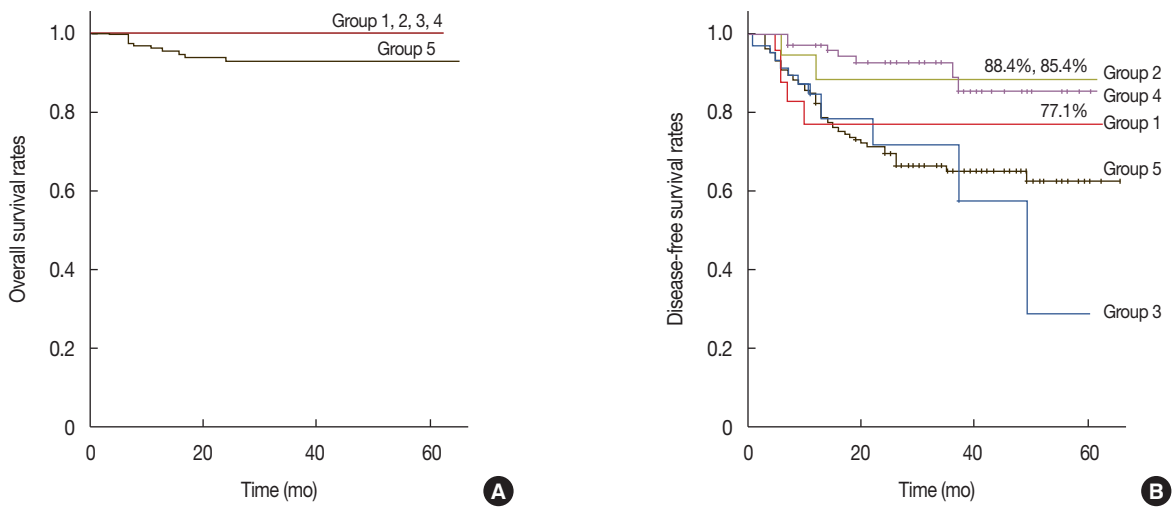

Figure 2. Kaplan-Meier survival curves for overall survival and disease-free survival in all groups. The *p*-value was calculated using log-rank test. The comparison of overall survival (A) in groups 1, 2, 3, 4, and 5 showed no statistical significant difference. There was a significant difference in the disease-free survival rate (B) between groups 1 and 4 (77.1% vs. 85.4%, $p=0.031$).

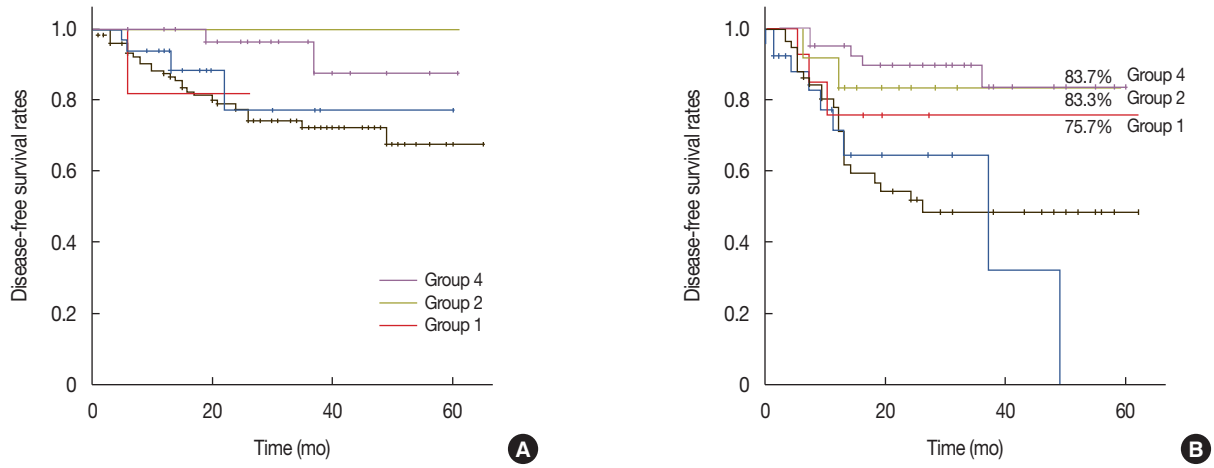

Figure 4. Kaplan-Meier survival curves for the disease-free survival of subgroups according to the hormone receptor status. The *p*-value was calculated using log-rank test. The disease-free survival curve of group 1 was early censored and could not be compared statistically in the hormone-positive subgroup (A). In hormone receptor-negative group (B), there was no statistical difference of recurrence between the group 1 versus group 2, and group 1 versus group 4 ($p=0.354$ and $p=0.401$).

alone group, two patients with HER2-positive tumors developed neurologic symptoms and were diagnosed with brain metastases within 6 months after surgery. Of the patients with recurrences in the SLNB alone group, axillary recurrence occurred in only one patient at 10 months postoperatively. The rate of axillary recurrence demonstrated no statistical differences among the groups (3.3%, 5.0%, and 1.3% for groups 1, 2, and 4, respectively, $p>0.05$). The rate of axillary recurrence was not significantly worse in the SLNB alone group in the axillary event-free survival analysis as shown in Figure 3.

In the subgroup analysis of disease-free survivals according to hormone receptor status, the survival curve of group 1 was early censored and could not be compared statistically in the hormone- positive subgroup. In hormone receptor-negative patients, there was no statistical difference of recurrence between group 1 versus 2, and group 1 versus 4 ($p=0.354$ and $p=0.401$, respectively) (Figure 4). In the multivariate analysis, no significant independent factors for recurrence were identified in the hormone receptor-negative subgroups.

DISCUSSION

During the last few years, there have been a number of clinical trials on the effectiveness and role of SLNB after NAC. According to their findings, SLNB after NAC seems to be an acceptable procedure, despite of varying degrees of false negative results. However, the reliability of SLNB following NAC for patients with initial nodal disease has been questioned, as the only available data have been from small series, reporting false-negative ratios ranging from 7% to 25%. Currently, ALND after NAC in patients with FNA-proven node-positive disease at presentation is recommended. However, the ALN metastases may have been eradicated by the chemotherapy in certain patients, who could consequently be spared ALND. Even in patients with nodal disease at presentation, sparing those patients the morbidity associated with axillary dissection would be desirable. Thus, we expect that the SLNB procedure could represent a restaging tool and aid in the proper management of the axilla in breast cancer patients with ALN metastasis before NAC.

Several reasons for avoiding SLNB after NAC have been suggested. Anatomical alterations of the lymphatic drainage may occur by disruption of the lymphatic vessels by the tumor, inflammation, or fibrosis, or due to blockage by necrotic and/or apoptotic cells. In addition, NAC can induce a nonuniform tumor regression in the axillary nodes [17-19]. However, these allegations of treatment-related alterations in lymphatic drainage have not yet been confirmed [20]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial is one of the largest studies published to date on SLNB after NAC [21]. A total of 428 patients underwent SLNB with concomitant ALND after NAC with an identification rate of 84.8% and a false-negative rate (FNR) of 10.7%. In addition, a meta-analysis of 21 studies, involving a total of 1,273 patients who received NAC followed by SLNB and ALND indicated an average identification rate of 91% and an FNR of 12% [22]. The ACOSOG Z1071 trial showed that the FNR of SLNB after NAC in patients with cN1 breast cancer and at least two SLNs identified at the time of surgery was with 12.6% higher than the expected threshold of 10% [23]. Herein, although all

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cases were cytologically proven positive ALNs at presentation, our study showed good results with an FNR of SLNB after NAC of 10.0% and an identification rate of 95.8%. These favorable findings may be the result of the dual-agent mapping technique used. The mean number of retrieved SLNs, including non-SLNs suspicious for metastasis, was 3. Therefore, technical factors are important to minimize the risk of incorrect nodal staging.

Straver et al. [24] analyzed responses to NAC in the axilla of patients with metastatic ALNs proven by cytology at presentation. They reported that a pCR of ALNs was more frequently found in patients with triple-negative tumors and HER2 positive tumors with a pCR of the primary tumor. Similarly, we also found that the luminal subtypes did not show significant differences in the pCR rates between the groups ($p > 0.05$).

Many studies on SLNB in a neoadjuvant setting used the FNR and identification rate as the endpoints. However, this may not be the best choice. Instead, looking at the regional recurrences when ALND is withheld may be the best endpoint to establish the safety and appropriateness of SLNB. The NSABP B-04 randomized trial of clinically node-negative patients found no significant differences in the survivals among three treatment arms, namely patients who underwent ALND, axillary radiation therapy, or no direct axillary treatment [25]. Bilimoria et al. [26] studied the differences in axillary recurrences and overall survival in pathologically node-positive breast cancer in patients who underwent SLNB with or without ALND, and found that all had clinically node negative disease posttreatment. There were no significant differences in the axillary recurrence and survival for SLNB alone versus ALND after a median follow-up of 63 months.

On the other hand, no long-term outcome data have yet been reported in patients with SLNB only after NAC with cytology proven node-positive disease before NAC. Despite of the relatively short follow-up period, our study found that there was no significant difference in axillary recurrence between the SLNB only and ALND groups.

There are a few limitations of our study that need to be addressed. First, no selection criteria were established, owing to the retrospective study design. However, the majority of patients classified as clinically node-negative after NAC were assigned to the SLNB group. Second, the relatively short follow-up period means that the subtype analyses cannot be considered definitive. Therefore, further follow-up is warranted. Lastly, only a small number of patients could be investigated, owing to the fact that ALND was the standard treatment in previous node-positive breast cancers.

In conclusion, SLNB performed after NAC in patients with initial node-positive breast cancer may help identify down-staging to negative nodal status and reduce the surgical morbidity of these patients by avoiding the need for standard ALND. Future studies with a large number of patients are needed in order to establish the safety of SLNB in conversion to clinically node-negative patients after NAC.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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