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ORIGINAL ARTICLE

Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer with axillary node metastasis: A survey of clinical practice

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Summary *Background:* A survey of breast surgeons was conducted to evaluate changes in clinical practice regarding sentinel node biopsy (SNB) among clinically node-negative patients after neoadjuvant chemotherapy for breast cancer with axillary node metastasis.
Methods: We conducted two surveys among 252 members of the Korean Breast Cancer Society. The questionnaire comprised a case presentation and two associated questions. The case outlined a woman diagnosed with right breast cancer; core needle biopsy had confirmed invasive ductal carcinoma and tumor size was 4 cm on imaging examination. Fine needle aspiration

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examination for axillary lymph node enlargement showed metastatic carcinoma. The patient underwent neoadjuvant chemotherapy and tumor size was decreased by 2 cm; axillary lymph node enlargement was not observed on palpitation or imaging examination. Finally, the patient underwent breast conserving surgery. Survey recipients were asked: 1. Would you perform SNB in this patient? 2. If you perform SNB and no axillary node metastasis is seen, would you perform additional axillary lymph node dissection (ALND)?
Results: The response rate was 28.2% (71/252) and 15.1% (38/252) in 2013 and 2017, respectively. For the first question, the SNB to ALND ratio increased significantly from 54% versus 46% in 2013 to 92% versus 8% in 2017 ($p < 0.001$). The proportion of surgeons performing no additional ALND versus additional ALND increased from 38% versus 54% in 2013 to 53% versus 37% in 2017, but did not reach statistical significance ($p = 0.1$).
Conclusions: These data show that application of SNB among clinically node-negative patients after neoadjuvant chemotherapy for breast cancer with node metastasis has increased among surgeons in Korea.

1. Introduction

Axillary lymph node (ALN) status is a key prognostic factor in patients with breast cancer. ALN staging and locoregional control can be performed by ALN dissection (ALND), but this procedure is associated with the potential for serious complications, such as lymphedema and nerve damage. Sentinel node biopsy (SNB), a procedure with fewer potential complications, has been proposed as an alternative. The accuracy of SNB has been confirmed in several clinical studies and SNB has become the standard surgical procedure for axillary staging in patients with clinically node-negative primary breast cancer.[1,2] The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32 showed a sentinel node identification rate of 97.2% and a false-negative rate of 9.8%, and demonstrated that the recurrence and survival rates for groups undergoing SNB or ALND were equivalent.[3,4]

Until recently, the effectiveness of SNB after neoadjuvant chemotherapy has been less clear. However, three prospective trials have now addressed this issue: the American College of Surgeons Oncology Group (ACOSOG) study Z1071, the SENTinelNeoAdjuvant (SENTINA) study, and the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SNFNAC) study.[3,5,6] In these studies, the detection rate with SNB after neoadjuvant chemotherapy was 80—93%, lower than that of the initial SNB. In addition, the false-negative rate was higher (9.6—14%) and was primarily affected by the number of sentinel lymph nodes removed. Therefore, due to the lower detection rate and higher false-negative rate than in primary surgery patients, the oncological safety of SNB-guided surgery for these patients remains uncertain, and the use and timing of SNB in patients with neoadjuvant chemotherapy remains the subject of considerable controversy.[7] However, a range of other studies, including the NSABP B-27 trial and several meta-analyses, have shown sentinel lymph node detection and false-negative rates after neoadjuvant chemotherapy to be comparable to those reported in patients with breast cancer who undergo upfront surgery.[7—11] Therefore, SNB offers the potential to decrease the need for axillary surgery in patients following neoadjuvant chemotherapy.[3,7] In the recent 2017 National Comprehensive Cancer Network (NCCN) guidelines, SNB is recommended in patients where needle biopsy has confirmed cancer in nodes before preoperative treatment but afterward they look and feel normal. Despite the available data, breast surgeons still tend to perform additional ALND even in the absence of ALN metastasis determined by SNB after neoadjuvant chemotherapy.

Therefore, in the current environment, where SNB for clinically node-negative breast cancer in the adjuvant setting has been popular, we aimed to determine changes in clinical practice regarding the application of SNB in breast cancer patients undergoing preoperative neoadjuvant chemotherapy by conducting a survey of members of the Korean Breast Cancer Society (KBCS).

2. Methods

We conducted two surveys among breast surgeons who were members of the KBCS. The questionnaire was circulated to 252 surgeons in 2013 (by post) and the same questionnaire was circulated again in 2017 (by e-mail). Surgeons who did not undergo breast cancer surgery were excluded from the analysis. The survey gathered information on the age of the surgeon and the number of beds in their hospital, as well as asking two questions based on a case presentation. The case outlined a woman diagnosed with right breast cancer; core needle biopsy had confirmed invasive ductal carcinoma and tumor size was 4 cm on imaging examination. Fine needle aspiration examination for ALN enlargement showed metastatic carcinoma, but PET/CT showed no systemic metastasis. The patient underwent neoadjuvant chemotherapy and tumor size was decreased by 2 cm; ALN enlargement was not observed on palpitation or imaging examination. Finally, the patient underwent breast conserving surgery. Survey recipients were asked: 1. Would you perform SNB in this patient? 2. If you perform SNB and no axillary node metastasis is seen, would you perform additional ALND?

Participants were also asked whether they participated in the multi-center RCT to investigate the survival rate

between patients in whom additional ALND was performed versus patients in whom no additional ALND was undertaken.

Statistical analysis was performed using the chi-square and Fisher's exact tests. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 20.0 (SPSS Inc., Chicago, USA).

3. Results

The survey response rate was 28.2% (71 of 252) and 15.1% (38 of 252) in 2013 and 2017, respectively. The average age of the respondents was 43 years (34—66 years) in 2013 and 45 years (33—65 years) in 2017 (Fig. 1). In 2013, the highest proportion of respondents were from university hospitals with fewer than 1000 beds (59.2%), followed by university hospitals with more than 1000 beds (18.3%); in 2017, university hospitals with more than 1000 beds accounted for 42.1% of respondents, followed by university hospitals with fewer than 1000 beds (39.5%; Fig. 2). There was no significant difference between the two groups ($p = 0.054$).

Regarding question 1, 'Would you perform SNB in this patient', the proportion of respondents stating that they would perform SNB rather than ALND increased significantly from 54% (versus 46% for ALND) in 2013 to 92% (versus 8% for ALND) in 2017 (Fig. 3, $p < 0.001$).

Regarding question 2, in the absence of sentinel node metastasis with SNB, the proportion of respondents indicating that they would not perform additional ALND was 38% in 2013 (versus 54% who would perform additional ALND) and increased to 53% (versus 37% who would perform additional ALND) in 2017, although there was no statistically significant differences in these data (Fig. 4, $p = 0.1$). We looked at differences in answers to each question according to the size of hospital (number of beds). Regarding question 1, 'Would you perform SNB in this patient', in 2013, breast surgeons working in hospitals under 500 beds prefer 100% (7) SNB preference, while surgeons working in hospitals over 1000 beds 100% (13 patients) answered that they only enforced ANLD. Surgeons working in hospitals with more than 500 beds and less than 1000 beds had 60.8% (31 participants) and 39.2% (20 participants), respectively ($p < 0.001$). On the other hand, surgeons working in hospitals with more than 1000 beds responded that all ALNDs would be implemented in 2013, but all of them in 2017 changed to SNB first (Table 1, $p = 0.198$).

Regarding question 2, in the absence of sentinel node metastasis with SNB, in 2013, all surgeons working in hospitals with over 1000 beds said they would carry out additional ANLD, while all surgeons at hospitals less than 500 beds did not ($p < 0.001$). However, the proportion of surgeons working in hospitals over 1000 beds decreased from 100% in 2013 to 12.5% in 2017, while the proportion of surgeons working in hospitals under 500 beds each had half the answers, respectively (Table 2, $p = 0.100$).

We asked, 'if there is no ALN enlargement on radiology and no ALN metastasis by SNB after preoperative neoadjuvant chemotherapy in breast cancer patients with ALN metastasis, do you require a safety rationale for additional ALND not being undertaken?' The vast majority (95%) answered 'yes' (data not shown).

The percentage of respondents who answered 'yes' to the question of whether they participated in the multicenter RCT to investigate the survival rate between additional ALND and 'no' to whether they would undertake additional ALND (question 2) increased slightly from 84.5% in 2013 to 92.1% in 2017. The reasons why doctors responded in this way were conflicting. One of the reasons is that 50% of patients do not require ALND. Also, in patients with confirmed ALN metastasis, there is a potential ethical issue associated with electing not to perform ALND in patients with no lymph node enlargement after neoadjuvant chemotherapy.

4. Discussion

Accurate staging and appropriate management of ALNs are important aspects in decision-making regarding the treatment of local, regional, and systemic breast cancer, and sentinel lymph node surgery is considered reliable for axillary staging in patients with node-negative early breast cancer.[12] Neoadjuvant chemotherapy is now often used to downgrade breast cancer prior to surgery; however, in patients with initial axillary lymph node metastasis, a complete ALND, regardless of the response to neoadjuvant chemotherapy, remains standard practice.[13] The recent 2017 NCCN guidelines included proposals for SNB implementation. Following neoadjuvant chemotherapy, residual axillary nodal disease is found in only 50—60% of breast

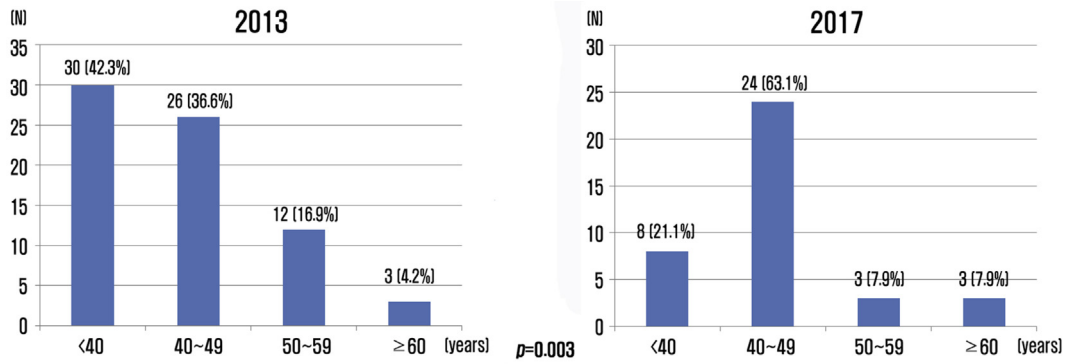

Figure 1 Age distribution of participants between 2013 and 2017.

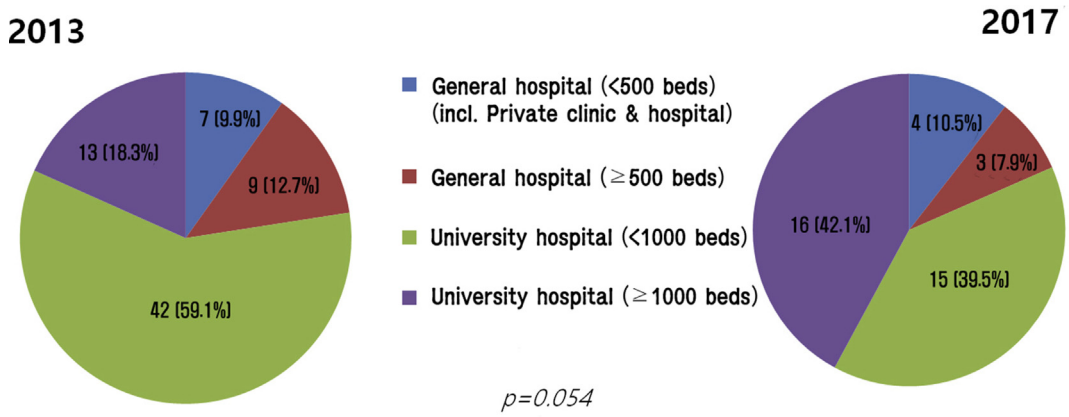

Figure 2 The characteristics of hospitals of breast surgeons.

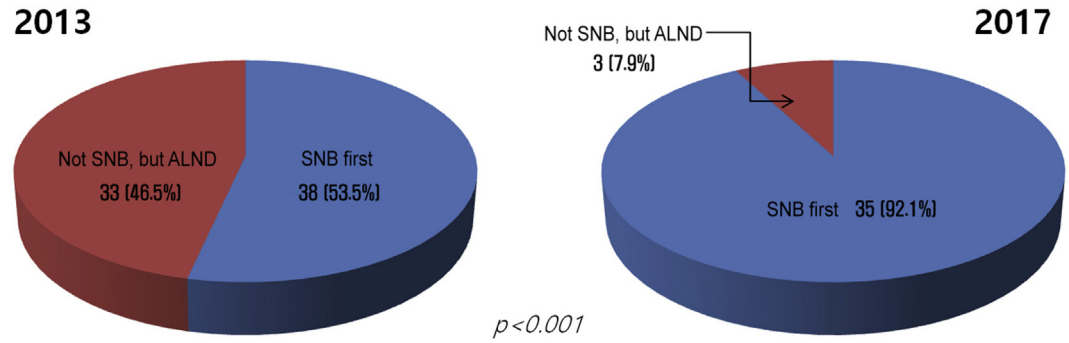

Figure 3 Methods for the evaluation of axillary stage in patients with axillary metastatic breast cancer after neoadjuvant chemotherapy.

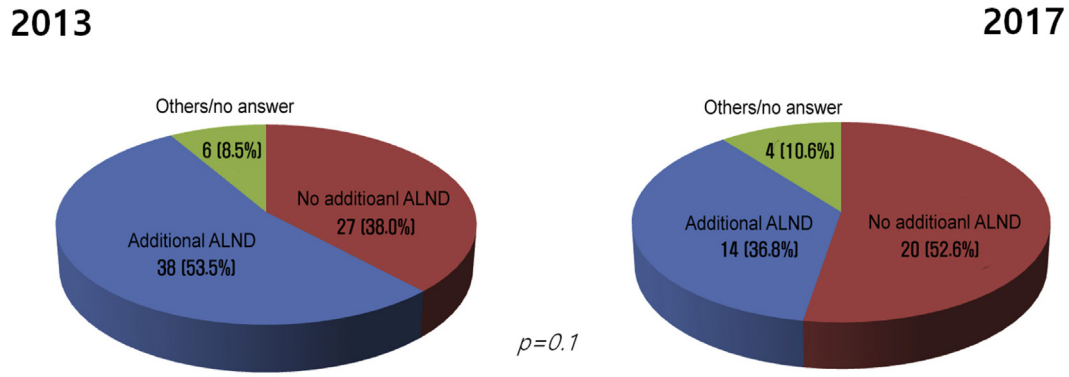

Figure 4 Addition of ALND without sentinel lymph node metastasis in axillary metastatic breast cancer after neoadjuvant chemotherapy.

cancer patients initially presenting with node-positive disease. While it is important to precisely determine the involvement of the axillary nodes after chemotherapy, evaluation often involves the removal of all nodes, thereby risking the potential morbidity associated with this procedure despite the fact that only a proportion of patients will benefit from it.[14,15]

Several reasons for avoiding SNB after neoadjuvant chemotherapy have been proposed, one being that anatomical changes in lymphatic drainage can occur due to destruction of the lymphatic vessels by tumors, inflammation, fibrosis, or blockage by necrosis.[16–18] However, these potential alterations related to lymphatic drainage have not yet been confirmed.[19] The NSABP B-27 trial included 428 patients who underwent SNB with concomitant ALND after neoadjuvant chemotherapy. This study reported a detection rate of 84.8% and a false-negative rate of 10.7%.[11] Also, the ACOSOG Z1071 trial showed that the false-negative rate associated with SNB after neoadjuvant chemotherapy in patients with node-positive breast cancer (and at least two sentinel lymph nodes identified at the time of surgery) was 12.6%.[5] In

Table 1 Methods for the evaluation of axillary stage in patients with axillary metastatic breast cancer after neoadjuvant chemotherapy according to the size of hospital.

Year	2013					2017				
Scale	<500 beds	500–1000 beds	≥1000 beds	total	*p*-value	<500 beds	500–1000 beds	≥1000 beds	total	*p*-value
SNB	7 (100%)	31 (60.8%)	0 (0%)	38 (53.5%)	<0.001	3 (75.0%)	16 (88.9%)	16 (100%)	35 (92.1%)	0.198
ALND only	0 (0%)	20 (39.2%)	13 (100%)	33 (46.5%)		1 (25.0%)	2 (11.1%)	0 (0%)	3 (7.9%)	
Total	7 (100%)	51 (100%)	13 (100%)	71 (100%)		4 (100%)	18 (100%)	16 (100%)	38 (100%)	

Table 2 Addition of ALND without sentinel lymph node metastasis in axillary metastatic breast cancer after neoadjuvant chemotherapy according to the size of hospital.

Year	2013					2017				
Scale	<500 beds	500–1000 beds	≥1000 beds	total	*p*-value	<500 beds	500–1000 beds	≥1000 beds	total	*p*-value
Add ALND	0 (0%)	14 (27.5%)	13 (100%)	27 (38.0%)	<0.001	2 (50.0%)	10 (55.6%)	2 (12.5%)	14 (36.8%)	0.100
No ALND	7 (100%)	31 (60.8%)	0 (0%)	38 (53.5%)		2 (50.0%)	7 (38.9%)	11 (68.8%)	20 (52.6%)	
Others	0 (0%)	6 (11.7%)	0 (0%)	6 (8.5%)		0 (0%)	1 (5.5%)	3 (18.7%)	4 (10.4%)	
Total	7 (100%)	51 (100%)	13 (100%)	71 (100%)		4 (100%)	18 (100%)	16 (100%)	38 (100%)	

addition, a meta-analysis of 21 studies, involving a total of 1273 patients who received neoadjuvant chemotherapy followed by SNB and ALND, indicated an average detection rate of 91% and a false-negative rate of 12%.[11] These results show a false-negative rate that is higher than the expected threshold of 10% and therefore form the basis of much decision-making by surgeons who perform ALND in breast cancer patients after preoperative neoadjuvant chemotherapy with ALN metastasis.

By contrast, data from the MD Anderson Cancer Center have demonstrated sentinel lymph node detection rates of 97.4% for women who underwent SNB after neoadjuvant chemotherapy and 98.7% for patients treated with upfront surgery. In addition, false-negative rates were similar at 5.9% versus 4.1%, respectively ($p = 0.39$).[7,9] Many other studies, and some meta-analyses, have also shown that sentinel lymph node identification rates and false-negative rates after neoadjuvant chemotherapy are comparable to those reported in patients with breast cancer who undergo upfront surgery.[10]

Long-term outcomes can be considered to be more important than the identification rate or false-negative rate in breast cancer patients. Bilimoria et al studied the difference in axillary recurrence and overall survival in pathologically node-positive breast cancer patients who underwent SNB with or without ALND, demonstrating that all were clinically node-negative after neoadjuvant chemotherapy.[20] After a median follow-up of 63 months, there were no significant differences in the axillary recurrence and survival rate for SNB alone versus ALND. Galimberti et al reported that 5 year overall survival rates were 93.3% in patients who were clinically node-negative before neoadjuvant treatment and 86.3% in initially node-positive patients ($p = 0.12$).[21] This study also showed that axillary failure only occurred in one patient (0.7%) among those who were initially clinically node-negative. These findings lead us to conclude that SNB is acceptable in node-negative patients after neoadjuvant treatment as the axillary disease rate is very low and outcomes did not differ between the two groups. Kang et al retrospectively assessed 1247 breast cancer patients with clinical conversion of ALNs from positive to negative following neoadjuvant chemotherapy. Sentinel biopsy-guided axillary surgery and ALND without SNB were associated with a similar rate of recurrence (4-year axillary recurrence-free survival: 97.8% versus 99.0%, respectively; $p = 0.148$); multivariate analysis also indicated that the two groups had no significant difference in axillary and distant recurrence-free survival (HR: 2.33, $p = 0.061$).

In light of the many differing opinions, decision-making can be challenging for breast surgeons. As the time between the publication of study results and subsequent implementation in the clinic can be lengthy, we conducted a survey to identify changing behavior among Korean breast surgeons, comparing clinical practice in 2013 with that in 2017. The proportion of surgeons preferring SNB was significantly increased from 53.5% in 2013 to 92.1% in 2017 ($p < 0.001$). By contrast, the proportion of surgeons electing not to perform ALND did not change as significantly (increasing from 38.0% in 2013 to 52.6% in 2017; $p = 0.1$). It was found that the results of various studies influenced the clinical decision-making of breast surgeons and currently many still perform additional ALND. This is possibly due to concerns regarding the potential decrease in survival rate or quality of life due to recurrence and secondary metastasis, and many surgeons may tend to adhere to traditional

treatment modalities, rather than adopting new treatment protocols.

Our study has several potential limitations. First, the survey was brief, being limited to five questions in order to ensure that the questionnaire could be completed quickly and thereby optimize the number of responses returned. Secondly, the scenarios were simple; we presented one case on which the treatment questions were based. However, the case did not include details of tumor histology, hormone receptor status, planned radiation tangents, or characteristics of the examined nodes, which are important considerations when determining whether or not to undertake ALND. Thirdly, the number of breast surgeons responding to the survey was relatively low and it was not confirmed whether the same surgeons responded to both surveys. To overcome these limitations and to obtain more representative data, a larger sample size from a wider range of medical institutions would be required.

In conclusion, these data showed a change in clinical practice relating to the implementation of SNB in clinically node-negative patients after neoadjuvant chemotherapy in breast cancer with node metastasis, with SNB increasingly being adopted in routine practice. In addition, although many breast surgeons perform additional ALND in node-negative patients, the proportion of surgeons electing not to perform this additional procedure is gradually increasing. A prospective randomized clinical trial is required to evaluate the clinical outcome of SNB versus conventional ALND in this patient population.

Conflicts of interest

The authors declare that they have no competing interests.

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