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Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy in a Patient with Operable Breast Cancer

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Abstract

Purpose. This study was undertaken to assess the feasibility of performing a sentinel lymph node biopsy (SLNB) for a patient with operable breast cancer after undergoing neoadjuvant chemotherapy (NAC).

Method. Between January 2002 and December 2003, women with primary breast cancer who had a breast tumor measuring larger than 3 cm in unilateral diameter were eligible for NAC. All patients who had completed NAC underwent lymphatic mapping with labeled ^{99m}Tc phytate on the day before surgery. Sentinel lymph node biopsy followed by a full axillary lymph node (AXLN) dissection (ALND) was performed in all patients. Sentinel lymph nodes (SLN) were sent for a frozen-section examination.

Results. The rate of SLN identification was 71%. Both the sensitivity and negative predictive value of SLNB were 100%. The false negative rate was 0%. When candidates for SLNB were restricted to patients with a breast tumor measuring less than 3 cm and clinically negative nodes after NAC, the rate of SLN identification increased to 93% from 71% while still maintaining the 0% false negative rate.

Conclusion. Sentinel lymph node biopsy after NAC is therefore considered to be a feasible and accurate method to predict the AXLN status in patients who have a breast tumor measuring less than 3 cm in unilateral diameter and a clinically negative AXLN status at the time of surgery after NAC.

Key words Breast cancer · Sentinel lymph node biopsy · Neoadjuvant chemotherapy

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Introduction

Neoadjuvant chemotherapy (NAC) has been evolved and increasingly used in the management of patients with wide stage breast cancer instead of postoperative adjuvant chemotherapy. Superior response rates have been achieved in studies evaluating the sequential use of docetaxel after anthracycline-containing regimens,[1,2]

One of the most important benefits of NAC is that it can downstage the primary tumor in most patients allowing the potential for extending breast conserving therapy (BCT) to patients with large tumors that would otherwise require a mastectomy. Furthermore, it also helps us to assess the response of the primary tumor to treatment. The pathological response to NAC significantly correlates with the long-term disease-free survival. It is now recognized that the accurate axillary lymph node (AXLN) status even after NAC is one of the most important predictors of the prognosis.[3–7] Information about the AXLN status is necessary when selecting the subsequent adjuvant systemic therapy and radiation therapy to improve the survival, even in patients treated with NAC. Unfortunately, although several authors have reported the feasibility of ultrasound examinations to assess the AXLN status, the surgical sampling technique is considered to be the only way to accurately predict the AXLN status.[8]

Axillary lymph node dissection (ALND) has indeed been established as a procedure to provide accurate information about the AXLN status and excellent regional tumor control in patients with wide stage breast cancer, but ALND is a major surgical treatment and results in an increase in ALND-associated complications including seroma formation, pain, nerve injury, infection, limitations of shoulder motion, and arm lymphedema which occur in from 6% to 30% of patients after ALND.[9,10] Furthermore, the benefit as far as an increased survival from ALND for breast cancer has not yet been established.[11,12] On the other hand, the National

Surgical Adjuvant Breast and Bowel Project (NSABP) study (protocol B-27) showed that the rate of the pathologically negative AXLN status in patients who had preoperatively undergone four cycles of the anthracycline-containing regimen followed by four cycles of docetaxel was 58.2%.[2] NSABP (protocol B-18) showed conversion of the clinically positive AXLN status to a pathologically negative status after NAC occurred in 38%.[13] Kuerer et al.,[6] and Rouzier et al.[5] reported that NAC resulted in a pathologically complete response of AXLN in 23% of the patients with cytologically proven positive node(s) at the time of diagnosis.[5,6] Apart from the impact of prophylactic ALND on survival, NAC results in an increasing population of patients who had no need to undergo a diagnostic ALND.

Sentinel Lymph Node Biopsy (SLNB) is a minimally invasive new procedure which is used as an alternative to ALND to stage the axilla. Several studies have demonstrated the accuracy of SLNB in predicting AXLN status and a reduction in the physical morbidity in patients with early breast cancer. However, it has been recognized as being applied to patients with a small breast tumor and clinically negative nodes.[14–23] Several studies on this concept have provided positive results and counter results, and thus the definitive indications and contraindications for SLNB after NAC have not yet been established.[24–30] In this study, we attempted to assess the feasibility and accuracy of SLNB after NAC.

The primary aim of this study was to evaluate the sensitivity, negative predictive value, and false-negative rate of SLNB after NAC. The secondary aim was to investigate the limiting factors for SLNB in patients after NAC by comparing the successful identification of SLNB and unsuccessful mapping.

Patients and Methods

Patients and Treatment

Between January 2002 and December 2003, 55 women with primary operable invasive breast cancer in whom the size of an unilateral breast tumor was larger than 3 cm in diameter received NAC and underwent lymphatic mapping and SLNB followed by a full ALND as a component of the surgical treatment for breast cancer approximately 2 weeks after the completion of NAC, if they had no evidence of distant metastatic disease, were not pregnant, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate cardiac, renal, hepatic, and hematologic functions. The diagnosis was established by a core needle biopsy of the primary tumor alone. Local institutional review boards approved the protocol, and all patients were required to sign an informed consent form before being enrolled onto the study. The patients and tumor characteristics before NAC are presented in Table 1.

Table 1. Patients and tumor characteristics before neoadjuvant chemotherapy

Characteristic		No. of patients
Total patients		55
Median age (years)	48 (24–70)	
Menopausal status		
Pre		22
Post		33
ER status		
Positive		18
Negative		37
Tumor status		
Median tumor size (cm)	4.5 (3.0–12.0)	
T2		33
T3		22
Clinical AXLN status		
Positive		22
Negative		33
Histology		
Invasive ductal		54
Invasive lobular		1

ER, estrogen receptor; AXLN, axillary lymph node

Neoadjuvant Chemotherapy

Six patients were treated with a 7-day cycle of docetaxel (TXT) (35 mg/m^2) and 49 patients with a 7-day cycle of paclitaxel (PTX) (80 mg/m^2). Each cycle consisted of 3 weeks of therapy followed by a 1-week treatment break. Twenty-six patients received three cycles of NAC, 25 patients had four cycles, 2 patients had two cycles, and 2 patients had eight cycles. In the patients treated with three cycles of NAC, the number of cycles and NAC agent were decided in accordance with ongoing clinical study about NAC at that time.

Nine (16%) patients had a clinical complete response (cCR) and 28 (51%) had a partial response (cPR). Despite the low rate of cCR in this study, all of the 9 patients with cCR achieved a pathological complete response (no residual in situ or invasive disease in the breast or axillary lymph nodes). The median clinical tumor size was reduced from 4.5 cm to 2.5 cm. Of 22 patients with positive clinical AXLN status, 12 (55%) were converted to a negative clinical AXLN status on physical and imaging examinations.

Localization and Identification of Sentinel Lymph Nodes

To localize the site of the SLNs and to confirm their number, all consecutive patients underwent lymphos-

cintigraphy as a prelude to SLNB (lymphatic mapping). One milliliter of radioactive tracer filtered ^{99m}Tc phytate acid labeled with sulfur colloid was usually injected in four 0.25-cc aliquots in separate sites around the peritumor on the day before surgery. Patients whose breast tumor was not palpable received the same injection in the subareolar area of the tumor-bearing breast. Anterior and anterior-oblique lymphoscintigraphy were subsequently performed to obtain the site and the number of lymphoscintigraphic projections as the radiographically identified SLNs approximately 3 h after radioactive injection. In this study, only lymph nodes that had both lymphoscintigraphic projections on the axilla area and high radioactivity as detected with an intraoperative gamma probe were identified with SLNs (successful mapping).

Even in patients with early breast cancer, SLNB has not been performed in our institute when no lymphoscintigraphic projections were detected in the axilla area. When the number of radioactive lymph nodes detected by the gamma-probe was more than that seen on the lymphoscintigraphic projections, all lymph nodes with the same level as the lymph node with the highest radioactivity were labeled as SLNs. However, converse cases (the number of removed lymph nodes as SLNs was less than the number of lymphoscintigraphic projections) were defined as no identification.

Pathology

Sentinel lymph nodes were immediately divided into small sections at a minimum of 2-mm intervals. Firstly, the face of each section was intraoperatively examined using the imprint technique. Secondly, each frozen section was intraoperatively obtained to confirm of the presence of malignant cells. The remaining frozen tissue was thawed, fixed, and embedded to produce a permanent section. Standard hematoxylin–eosin (H&E) staining examination was performed subsequently.

All of the SLNs negative on frozen and permanent section were subjected to serial step sectioning and immunohistochemical staining (IHC) with an anticytokeratin antibody cocktail (MAK-6; Ciba-Corning, Alameda, CA, USA) as a definitive pathological examination. Non-SLNs were examined with a standard technique. In non-SLNs, IHC was not performed unless routine H&E detected suspicious but not diagnostically malignant cells.

Statistical Analysis

The correlation between SLN identification and categorical clinicopathologic factors such as AXLN status before or after NAC, multifocality, and menopausal status was assessed with Fisher's exact test. The correlation between SLN identification and continuous and ordered categorical clinicopathologic factors, such as breast tumor size before or after NAC, body mass index (BMI), and age was assessed with the Mann–Whitney nonparametric test and Fisher's exact test. $P \leq 0.05$ was considered to be statistically significant.

Results

Sentinel Lymph Node Identification and Pathological Examination

In 13 of the 55 patients, lymphoscintigraphy revealed no uptake in the radioactivity to the axilla and most of lymphoscintigraphic projections remained around the breast tumor. In these thirteen patients, none of the SLNs could be identified and isolated. In three patients with successful mapping, no lymph node labeled as SLN could be found with the gamma probe. At least one SLN was identified in 39 (71%) of the 55 patients. In 16 of the 39 patients, the number of radioactive lymph node labeled as SLNs was more than that of lymphoscintigraphic projections. The median number of SLN examined in the 39 SLN specimens was 1 (range, 1–8). In 20 patients, there was one SLN, in 12 patients two SLNs, and in 7 three or more SLNs. A total of 66 SLNs existed at the anatomic level of the axilla.

Of the 39 patients whose SLNs were examined intraoperatively by usual frozen section, 22 were negative and 17 were positive. In 5 of the 17 patients with positive SLNs, the SLN was the only positive lymph node. In these five patients, two patients had micro-metastasis on usual frozen section examinations, measuring 0.2 mm and 0.5 mm in size, respectively. Among these 22 patients, only one SLN negative on frozen section was found to contain micro-foci (0.05 mm) on definitive pathological examinations with serial step sectioning and IHC staining. Therefore, of the 39 patients, 21 were negative and 18 were positive (Table 2).

Table 2. Sentinel lymph node biopsy

Variable	No. of patients
SLNB procedures	55
SLN identification	39 (71%)
No SLN identification	
Successful mapping	3
Unsuccessful mapping	13
Positive SLNs	
Micrometastasis	18
Detected by frozen section	2
Detected by IHC examination	1
SLN-only positive node	5

SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; IHC, immunohistochemical staining

Pathologic Status of SLNs and AXLNs

Among the 55 patients, a total of 924 AXLNs were removed and examined with a standard technique. The median number of AXLNs examined in the 55 dissections was 16 (range, 11–25). In 21 patients with negative SLNs, the corresponding AXLNs were completely negative.

The overall concordance between SLN and AXLN was 100%. The false-negative rate was 0% (Table 3).

Statistical Analysis of the Correlation Between the Clinicopathologic Factors and SLN Identification

Univariate tests of the correlations between various clinicopathologic factors and SLN identification were analyzed, and showed that the breast tumor size after NAC and the AXLN status after NAC were significantly associated with SLN identification. The initial breast tumor size, initial AXLN status, age and menopausal status had no effect on SLN identification. A significant correlation was found between SLN identification and BMI (Table 4).

Table 3. Pathologic status of SLNs and AXLNs

	AXLNs		
SLNs	Positive	Negative	Total
Positive	18	Not applicable	18
Negative	0	21	21
Total	18	21	39

Sensitivity = (No. of patients with positive SLNs)/(No. of patients with AXLN metastasis) = 100%
Specificity = (No. of patients with negative SLNs)/(No. of patients with no AXLN metastasis) = 100%
Overall accuracy = (No. of patients with true positive and true negative SLNs)/(No. of patients with SLN identification) = 100%
Negative predictive value = (No. of patients without AXLN metastasis)/(No. of patients with negative SLNs) = 100%
False negative rate = (No. of patients with negative SLNs)/(No. of patients with AXLN metastasis) = 0%

Discussion

Our results showed SLNB to be a feasible method for predicting the accurate AXLN status even in patients treated with NAC. In the current study of 55 patients who underwent SLNB followed by complete ALND after NAC, SLNs were identified in 39 (71%) of the 55 patients. This rate of 71% of SLN identification was lower than that reported in recent studies of early-stage breast cancer or locally advanced breast cancer after NAC.[14–23] Recent studies on early-stage breast cancer have demonstrated that SLNs were able to be identified in more than 90% of cases with false negative rates ranging from 2% to 10%.[14–23] Breslin et al.[20] and Haid et al.,[23] who approved of SLNB after NAC, showed that the SLN identification rate after NAC was more than 84% with less than 12% of false negative rate.[24]

The lower rate of SLN identification in this study was mostly caused by a failure to localize the SLNs on lymphoscintigraphy (unsuccessful mapping). The number of removed lymph nodes as SLNs was less than the number of lymphoscintigraphic projections in three patients. In 13 (81%) of the 16 patients in whom SLNs

Table 4. Factors affecting SLN identification

	SLN identification	No SLN identification	*P* Value
Patients (*n*)	39	16	
Median age (years)	48	49	NS*
Menopausal status (*n*)			NS**
Pre	15	7	
Post	24	9	
Median tumor size (cm)			
Before NAC	4.3	5.0	NS*
After NAC	2.2	5.0	0.0003*
Clinical AXLN status (*n*)			
Before NAC			NS**
Positive	22	11	
Negative	17	5	
After NAC			0.048**
Positive	4	6	
Negative	35	10	
BMI (*n*)			0.008**
<25	32	8	
≥25	7	9	
Multifocality (*n*)	3	4	NS**

NAC, neoadjuvant chemotherapy; BMI, body mass index = weight/height^2. Women who have a BMI more than 25 were considered to be preobese
*Mann–Whitney nonparametric test; **Fisher's exact test; NS, not significant

could not be identified, lymphoscintigraphy revealed no uptake radioactivity to the axilla and most of the lymphoscintigraphic projections remained around the breast tumor as the initially injected four hot spots. Nine of these 13 patients with unsuccessful mapping had an extensive breast tumor larger than 5 cm with or without multifocality, a lot of positive nodes, or both after NAC. These patients with large tumors were categorized as poor responders to NAC. In two patients in whom a small breast tumor less than 3 cm and pathologically negative nodes were noted, one of them had a subepidermal invasion of breast tumor and the other had a BMI of 35.5. In one patient with a small breast tumor and pathologic negative nodes, this unsuccessful mapping occurred early in this study, therefore if SLNB had been performed by the two-mapping method (blue dye in combination with technetium-labeled sulfur colloid), then the SLNs might have been identified. In these patients with unsuccessful mapping, the abovementioned locally advanced factors might cause occlusion of the lymphatic flow to the SLNs, lymphostasis of the breast, or limited migration of the radioactive tracer, which resulted in the failure of the lymphatic network from the breast tumor or the SLNs themselves to take up the radioactive tracer. In three of the 16 patients in whom SLNs could not be identified, lymphoscintigraphic projections were slightly detected around the axilla area on the day before surgery, while none of the lymph nodes could be found as labeled SLNs with the gamma probe. All of three patients also had locally advanced factors which were similar to those of patients with unsuccessful mapping. In these cases, decreasing the capacity of SLNs to uptake and retain the radioactive tracer might have had an effect on the failure of SLN identification, because SLNs were placed by metastatic foci. The remaining one patient with a small breast tumor and clinically negative nodes after NAC, in whom lymphoscintigraphic projection was detected not on the axilla but on the supraclavicular area, was confirmed to have 13 pathological positive nodes after surgery. In this case, tumor emboli might occlude the lymphatic flow to the SLNs and develop an alternative route to the original lymphatic channel.

A univariate analysis demonstrated that the breast tumor size and AXLN status after NAC were significantly associated with SLN identification, while the initial breast tumor size, initial AXLN status, patient age, multifocality, or menopausal status were not inversely associated with SLN identification. The reason why our data indicated no association between multifocality and SLN identification might be due to the effect associated with multifocality being hidden behind that of the size of the large breast tumor, because almost all of the large breast tumors in patients with unsuccessful mapping took the form of multifocality. It has been established that extensive multifocal breast tumors or clinically positive nodes were not suitable indications for SLNB, because multifocality was likely to involve an extended area of the lymphatic network of the breast.[4,17] However, as NAC has been increasingly used in patients with breast cancer, the proportion of patients will increase in whom a large breast tumor will be turned into a small breast tumor with multifocality caused by the unequal effect of NAC on breast cancer cells. The optimal treatment of SLNB in a small breast tumor with multifocality is therefore noteworthy.

Krag et al.[12] and Nason et al.[21] reported that an increase in age beyond 50 years was associated with the failure to identify SLNs, which was not seen in this study. In regard to the correlation between increasing age and SLN identification, the interpretation of Krag et al. was that in older patients, the capacity of lymph nodes to retain the radioactive colloid might be decreased, because lymph nodes were replaced by fat in elderly persons. In addition, McMaster et al.[17] suggested that a fat-replaced postmenopausal breast might be related to the ability of the radioactive tracer to be taken up by the lymphatic system.

In this study, the SLN identification rates were significantly lower in patients with a BMI of higher than 25. Unsuccessful mapping was seen in 56% of the patients with a BMI higher than 25. In patients with a higher BMI, a radioactive tracer might not be taken up well by the lymphatic system according to the theory of fat-replaced postmenopausal breast. If a higher BMI or fat-replaced breast reduced the ability of the lymphatic system to take up the radioactive tracer, some modification of the mapping technique such as increasing the injection volume or breast massage after injection might improve the SLN identification rate.[15,23] In 16 of the 39 patients with SLN identification, the number of radioactive lymph nodes was higher than that of the lymphoscintigraphic projection. We hypothesized that not only the slower migration of the radioactive tracer but also an inappropriate technique such as the timing of lymphoscintigraphy, or the volume or quality of the radioactive tracer might have some influence on this phenomenon.[16]

To determine which patients treated with NAC were eligible to be offered SLNB, our study contained a significant proportion of patients who were considered to be ineligible for SLNB because of breast tumor size, AXLN status, multifocality, or all of these. When candidates for this procedure were restricted to within the patients who had both clinically negative nodes and a solid breast tumor measuring less than 3 cm in size without skin invasion and multifocality at the time of surgery, the SLN identification rate was able to rise to 93% from 71%. This SLN identification rate of 93% in the 29 selected patients is comparable to that reported

in other current studies about SLNB in early-stage breast cancer patients.[18,19]

On the other hand, another most critical limiting factor of SLNB is the false negative rate (the proportion of patients with axillary nodal metastasis who are found, incorrectly, to have histologically negative SLNs). Although an acceptable false negative rate in SLNB has yet to be established, the technique of SLNB with a false negative rate of less than approximately 5% seemed to be recognized as an accurate and effective technique.[18,19] No false negatives were seen in this study. Nason et al., however, suggested that NAC was associated with an unacceptably high rate (33%) of false negative SLNs and, thus, resulted in inaccurate staging of the axilla for patients with breast cancer after NAC.[21] Similarly, Anderson et al. concluded that the use of SLNB was contraindicated after NAC on account of the high rate of false negative (25%).[26] There are several reasons why false negatives occur in patients with SLNB after NAC. One of the causes for a false negative finding is mislabeling of the non-SLNs as SLNs because of alternation of the original lymphatic channels after occlusion of the lymphatic flow to the SLNs. Neoadjuvant chemotherapy itself is also likely to cause false negatives, because when metastatic deposits within each lymph node include SLNs, which do not identically respond to NAC, it is possible that residual metastatic foci exist in non-SLNs but not in SLNs. In addition, Veronesi et al. recommended that SLNB should not be used in cases of extensive multifocal tumors, because multifocal tumors were likely to involve more than one lymphatic trunk from the mammary gland to the axillary nodes, which might give rise to skip metastasis.[16,29]

Although the influence of micrometastasis on the overall survival remains controversial, the ability to find the micrometastasis also has played an important role in SLNB.[4,31] In 29 (12%) of the 240 patients in our prior study about SLNBs in early-stage breast cancer, SLNs were found to contain micrometastasis (<2 mm). Of these 29 patients with micrometastasis, their presence in 15 patients was confirmed intraoperatively by a frozen section examination and in 7 patients by a permanent section examination with H&E staining. In the remaining 7 patients, SLNs negative on H&E examination were found to contain micrometastasis measuring less than 0.4 mm on serial sectioning and IHC examination. These results were similar to those reported by Giuliano et al.[19] and Veronesi et al.[29] Moreover, in 13 patients with micrometastases smaller than 0.4 mm in our prior study on routine SLNB, the corresponding AXLNs were found to contain no metastasis on the same examination.

Therefore, we have usually confirmed the SLN and AXLN status without serial sectioning and an IHC examination, which was in agreement with the study by Giuliano et al.[19] In this study, when all of 36 negative SLNs on frozen section examination in 22 patients with negative SLNs on frozen examination were confirmed by additional serial sectioning and an IHC examination, only one SLN was found to contain any microfoci (0.05 mm). Immunohistochemical staining was not used to examine all of the AXLNs, while we concluded that no metastasis existed in all of those AXLNs corresponding to SLNs which were negative on H&E staining, in accordance with the results of our prior study on SLNBs in early-stage breast cancer. This rate of 5% (1 of 19 patients), which is similar to the result reported by Fisher et al., thus meant a pathologically false negative; we, however, considered that this pathological false negative rate and the size of the micrometastases were enough to justify the use of SLNB after NAC to decide whether or not to perform ALND.

The accurate assessment of AXLN status with imaging and physical examination was not wholly satisfactory, therefore, the removal and histological examination of AXLN have been considered to be the gold standard for determining whether lymph node metastasis has occurred. However, ALND carries disadvantages. If the SLNB concept was able to be applied to patients treated with NAC, our 21 (49%) of 39 patients with negative SLNs ought in retrospect not only to have been able to avoid ALND but also to have been able to benefit from NAC. In other words, it is not going to far to say that in these 21 patients after NAC an unnecessary invasive operation was performed. Judging from this figure, we reasonably considered that the benefits of SLNB after NAC were likely to sufficiently exceed the unsolved problems associated with this approach, such as false negatives, especially in patients in whom further treatment therapy after NAC has already been decided.

In conclusion, our study demonstrated that SLNB was a feasible and accurate method to predict the AXLN status even in patients with operable breast cancer after NAC. The identification of SLNs was affected by breast tumor size after NAC, and the nodal status not at diagnosis but at surgery. When candidates for SLNB were restricted, the rate of SLN identification was able to increase from 71% to 93% while still maintaining the 0% false negative rate. Our findings suggested that SLNB could thus be performed in patients who had a small breast tumor which decreased to less than 3 cm in size and showed a clinically negative AXLN status at the time of surgery after NAC. Our observations in the present study were based on a small number of patients, so a prospective randomized trial and long-term follow-up is necessary in order to answer this question and to elucidate the optimal techniques for performing SLNB after NAC.

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