

## Original Article



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# Sentinel Lymph Node Biopsy in Breast Cancer Patients With Pathological Complete Response in the Axillary Lymph Node After Neoadjuvant Chemotherapy

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## ABSTRACT

**Purpose:** Sentinel lymph node biopsy (SLNB) alone following neoadjuvant chemotherapy (NAC) remains controversial in patients with breast cancer who are initially lymph node-positive. The present study aimed to evaluate the impact of SLNB and axillary lymph node dissection (ALND) on breast cancer recurrence and survival in patients who converted from lymph node-positive to pathological node-negative (ypN0) after NAC.

**Methods:** This single-center retrospective study included 223 patients who converted to axillary lymph node-negative status after NAC and underwent breast and axillary surgery between January 2006 and December 2015. This study compared the overall survival (OS), disease-free survival (DFS), ipsilateral axillary lymph node recurrence rates and incidence of postoperative complications, especially, arm lymphedema and shoulder stiffness between SLNB and ALND.

**Results:** This study included 223 patients with axillary pathological complete response (pCR) after NAC and surgery. The SLNB and ALND groups included 94 and 129 patients, respectively. The median follow-up time was 57 (range, 6–155) in the SLNB group and 99 (range 2–159) months in the ALND group. The corresponding 5-year OS and DFS rates were 96.3% and 94.2% ( $p = 0.392$ ), and 89.2% and 86.4% ( $p = 0.671$ ), respectively. Four patients (4.3%) in the SLNB group and nine (7.0%) in the ALND group developed locoregional recurrences. Ipsilateral axillary lymph node recurrence and distant metastasis were observed in one (1.1%) and three (2.3%) patients, and in 10 (10.6%) and 11 (8.5%) patients, respectively. Patients in the ALND group were more likely than their SLNB counterparts to experience complications, such as shoulder stiffness (9 [7.0%] vs. 4 [4.3%] patients,  $p = 0.57$ ). The rate of lymphedema in the ALND group was three times that in the SLNB group (35 [27.1%] vs. 8 [8.5%] patients,  $p < 0.001$ ).

**Conclusion:** As an alternative to ALND, SLNB has oncological safety in patients with axillary pathological complete response after NAC.

**Keywords:** Breast Neoplasms; Lymphatic Metastasis; Neoadjuvant Therapy; Sentinel Lymph Node Biopsy; Survival Rate

**Conflict of Interest**

The authors declare that they have no competing interests.

**Author Contributions**

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**INTRODUCTION**

Neoadjuvant chemotherapy (NAC) is a standard treatment for locoregionally advanced breast cancer as it can shrink the primary tumor and alleviate axillary lymph node involvement. NAC is commonly used in patients with stage II or III breast cancer and often result in, axillary pathological complete response (pCR). According to previous studies, after NAC, an axillary pCR is achieved in 20%–42% of initially node-positive patients [1-4]; this rate increases to 74% in patients treated with concurrent trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive breast cancer [5]. Axillary lymph node dissection (ALND) after NAC is the standard treatment for axillary surgery. However, current guidelines for the management of patients with complete response in the axillary nodes after NAC are not well defined. The 2014 American Society of Clinical Oncology guidelines recommend sentinel lymph node biopsy (SLNB) for early-stage breast cancer (T1/T2) with lymph node-negative (cNO) axilla [6]. Subsequently, axillary treatment is shifting to de-escalation therapy.

Several studies including NSABP-27 and GANEA have shown that SLNB after NAC in patients with cNO axilla is a feasible treatment option and that additional axillary treatment is not necessary for those with negative sentinel lymph nodes (SLNs) [7-9]. However, in patients with a clinically axillary lymph node-positive (cN+) patients who achieve clinical complete response (ycNO) after NAC, SLNB as axillary surgery remains controversial due to its high false-negative rate (FNR) and low SLN identification rates. Three major prospective studies, ACOSOG-Z1071, SENTINA, and SN-FNAC, evaluated women with node-positive disease who converted to clinically node-negative disease after NAC and underwent SLNB or axillary dissection. These studies suggest that SLNB is feasible in patients who convert to lymph node-negative disease following NAC if the technical aspects such as retrieval of three or more SLNs and use of dual mapping methods are well supplemented for a sufficiently low FNR [10-12]. Nevertheless, it is conceivable that false negative SLNB may lead to poor outcomes such as recurrence and decreased survival rates, due to the presence of occult residual disease.

Our study aimed to evaluate the oncologic safety of SLNB as an alternative to ALND by comparing outcomes according to the type of axillary surgery in final ypNO patients among patients who converted to clinically node-negative (cNO) after NAC.

**METHODS**

This was a retrospective study of patients with initially axillary lymph node-positive breast cancer who underwent surgery after NAC at our institution (details redacted for peer review) during 2006–2015. The study was approved by the Institutional Review Board (IRB No. NCC2021-0016). The need to obtain informed consent from the patients was waived due to the retrospective nature of the study.

We included women with clinical stage II–III (cN+) primary invasive breast cancer according to the American Joint Committee on Cancer (AJCC) cancer staging system who converted to clinically node-negative (cNO) status after NAC and were finally confirmed to be ypNO.

Patients with inflammatory breast cancer or distant metastasis and those who had previously undergone axillary surgery and radiation therapy were excluded from this study. In addition,

to ensure comparability of the prognosis, we excluded patients with positive axillary lymph nodes that were, pathologically confirmed after surgery.

A total of 223 patients with axillary pCR (ypN0) after NAC were divided into a SLNB (SLNB only or additional node sampling) group (n = 94) and an ALND group (n = 129), according to the axillary surgery method used and treatment outcomes were compared between these groups. To compare outcomes according to whether additional ALND was performed in patients who were sentinel node-negative on SLNB, a total of 165 patients were classified into subgroups, excluding 58 patients who failed sentinel node mapping in the ALND group. The subgroups were divided into an SLNB alone group (n = 94) and an additional ALND group (n = 71). The SLNB alone group was the same as the main group and for the additional ALND group, only patients who underwent successful sentinel node mapping in the main ALND group were selected. As with the main group, we compared outcomes and complications between subgroups.

ALND indications included failure of sentinel lymph node mapping, confirmed lymph node enlargement in the intraoperative field, or high-level (level II or above) initial axillary lymph node metastasis. In addition, even if sentinel node frozen biopsy findings were negative, additional ALND was performed according to the judgement of the five involved surgeons based on the presence of palpable lymph nodes or concerns about the possibility of residual disease due to the initial status.

SLNB was performed at our center using a radioisotope (RI). When the RI signal was not confirmed, the dual method with blue dye was used; in this study the dual method was used in eight cases.

### Statistical analyses

Data were retrospectively collected from the electronic medical records of patients treated between January 2006 and August 2020, and included information on surgery, neoadjuvant, and adjuvant therapy types, and follow-up findings. The purpose of this study was to compare the overall survival (OS), disease-free survival (DFS), and rate of ipsilateral axillary lymph node recurrence according to the type of axillary surgery. In addition, we evaluated the incidence of postoperative side effects, especially, arm lymphedema and shoulder stiffness. The  $\chi^2$  and Fisher's exact tests were used to compare the categorical variables between groups.

Survival was calculated from the date of surgery to the date of any event or the most recent follow-up, whichever occurred first. OS was defined as the time from surgery to death due to any cause. DFS was defined as the time to disease recurrence or metastasis after surgery. Locoregional recurrence was defined as recurrence in the ipsilateral breast, ipsilateral axillary, or regional lymph nodes. Distant recurrence was defined as recurrence in any other region. Survival and cumulative incidence rates were compared between the SLNB and ALND groups using the Kaplan-Meier method and log-rank test. Results were regarded as statistically significant at a *p*-value of  $\leq 0.05$ . We also applied the multivariate Cox proportional hazards model and assessed the influence of axillary surgery methods on OS and DFS after adjusting for tumor characteristics such as initial clinical T stage, initial clinical N stage, and tumor subtype, which are categorical variables. All statistical analyses were performed using R version 3.6.2 (R Development Core Team, Vienna, Austria, <https://www.r-project.org/>).

## RESULTS

### Baseline characteristics

This study included 223 patients with axillary pCR (ypN0) after NAC and surgery. The SLNB and ALND groups included 94 and 129 patients, respectively (Table 1). The median age of all patients was 47 (range, 26–75) years, and a total of 58 (26%) patients were aged < 40 years. All patients had clinical axillary lymph node-positive (N+) disease at initial staging, as assessed imaging, including breast sonography or magnetic resonance imaging. Most patients (approximately 80%) had stage N1 or N2 disease. All included patients had converted to cN0 disease, which

**Table 1.** Characteristics of the 223 women enrolled in the trial

| Characteristics            | Study group                   |               |                               |         |
|----------------------------|-------------------------------|---------------|-------------------------------|---------|
|                            | All (n = 223)                 | SLNB (n = 94) | ALND (n = 129)                | p-value |
| Age (yr)                   | 47 [26–75]                    | 46 [29–69]    | 48 [26–75]                    | 0.25    |
| Young age (< 40)           | 58 (26.0)                     | 27 (28.7)     | 31 (24.0)                     |         |
| 40–49                      | 82 (36.7)                     | 38 (40.4)     | 44 (34.1)                     |         |
| 50–59                      | 58 (26.0)                     | 23 (24.5)     | 35 (27.1)                     |         |
| 60–69                      | 22 (9.9)                      | 6 (6.4)       | 16 (12.4)                     |         |
| 70 ≤                       | 3 (1.4)                       | 0 (0)         | 3 (2.3)                       |         |
| Initial clinical T stage   |                               |               |                               | 0.70    |
| T1                         | 16 (7.2)                      | 6 (6.4)       | 10 (7.7)                      |         |
| T2                         | 140 (62.8)                    | 59 (62.8)     | 81 (62.8)                     |         |
| T3                         | 46 (20.6)                     | 22 (23.4)     | 24 (18.6)                     |         |
| T4                         | 21 (9.4)                      | 7 (7.4)       | 14 (10.9)                     |         |
| Initial clinical N stage   |                               |               |                               | 0.01    |
| N0                         | 0 (0)                         | 0 (0)         | 0 (0)                         |         |
| N1                         | 88 (39.5)                     | 48 (51.0)     | 40 (31.0)                     |         |
| N2                         | 94 (42.1)                     | 31 (33.0)     | 63 (48.8)                     |         |
| N3                         | 41 (18.4)                     | 15 (16.0)     | 26 (20.2)                     |         |
| Histologic finding         |                               |               |                               | 0.83    |
| Invasive lobular carcinoma | 2 (0.9)                       | 1 (1.1)       | 1 (0.8)                       |         |
| Invasive ductal carcinoma  | 221 (99.1)                    | 93 (98.9)     | 128 (99.2)                    |         |
| Pathological T stage       |                               |               |                               | 0.12    |
| ypT0                       | 78 (35.0)                     | 25 (26.6)     | 53 (41.1)                     |         |
| ypTis                      | 14 (6.3)                      | 8 (8.5)       | 6 (4.7)                       |         |
| ypT1                       | 93 (41.7)                     | 43 (45.7)     | 50 (38.7)                     |         |
| ypT2                       | 32 (14.3)                     | 17 (18.1)     | 15 (11.6)                     |         |
| ypT3                       | 4 (1.8)                       | 1 (1.1)       | 3 (2.3)                       |         |
| ypT4                       | 2 (0.9)                       | 0 (0)         | 2 (1.6)                       |         |
| Lymph node status          |                               |               |                               |         |
| Retrieved sentinel node    | 1.7 ± 1.6 (2.3 <sup>*</sup> ) | 2.2 ± 1.2     | 1.4 ± 1.8 (2.5 <sup>†</sup> ) | < 0.00  |
| Retrieved lymph node       | 7.2 ± 5.5                     | 2.7 ± 1.5     | 10.5 ± 5.0                    | < 0.00  |
| Tumor subtype              |                               |               |                               | 0.11    |
| HR+/HER2+                  | 36 (16.1)                     | 9 (9.5)       | 27 (21.0)                     |         |
| HR+/HER2–                  | 74 (33.2)                     | 31 (33.0)     | 43 (33.3)                     |         |
| HR–/HER2+                  | 29 (13.0)                     | 15 (16.0)     | 14 (10.8)                     |         |
| TNBC                       | 84 (37.7)                     | 39 (41.5)     | 45 (34.9)                     |         |
| Breast surgery             |                               |               |                               | 0.59    |
| BCS                        | 174 (78.0)                    | 75 (79.8)     | 99 (76.7)                     |         |
| Mastectomy                 | 49 (22.0)                     | 19 (20.2)     | 30 (23.3)                     |         |
| Radiotherapy               |                               |               |                               | 0.78    |
| Yes                        | 218 (97.8)                    | 93 (98.9)     | 125 (96.9)                    |         |
| No                         | 5 (2.2)                       | 1 (1.1)       | 4 (3.1)                       |         |

Values are presented as median [range], number (%), or mean ± standard deviation.

SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; HR+/- = hormone receptor-positive/-negative; HER2+/- = human epidermal growth factor receptor 2-positive/-negative; TNBC = triple negative breast cancer; BCS = breast conserving surgery.

\*The median number of retrieved SLNs for a total of 165 patients, excluding 58 people who immediately proceeded with ALND without identification of the sentinel node. †The average value of the retrieved sentinel node of 71 patients was calculated, excluding 58 patients who immediately performed ALND.

was assessed using physical examination and imaging at the end of NAC. Most patients received the AC-T regimen consisting of doxorubicin, cyclophosphamide and paclitaxel for NAC. Breast conserving surgery and mastectomy was performed in 174 (78.0%) and 49 (22.0%) patients, respectively. After surgery, five patients refused adjuvant treatment and 218 patients received radiation therapy. Postoperative pathological findings showed that 35.1% and 45.8% of patients in the SLNB and ALND groups, respectively, had breast pCR and ypTis ( $p = 0.12$ ).

### Survival outcomes

The median follow-up period was 77 (range, 2–159) months for all patients. During the study period, there were four (4.3%) and nine (7.0%) deaths from breast cancer in the SLNB and ALND groups, respectively. There were three deaths from other causes in the ALND group, resulting in an overall death rate of 7.2% (**Table 2**). Loco-regional recurrence was observed in four (4.3%) and nine (7.0%) patients in the SLNB and ALND groups, respectively; ipsilateral axillary lymph node recurrence was observed in one and three patients in each group, respectively. Distant metastasis occurred in 10 (10.6%) and 11 (8.5%) patients in the SLNB and ALND groups, respectively (**Table 2**). The overall 5-year OS rate was 95.1% (95% confidence interval [CI], 92.2%–98.1%); the corresponding rates for the SLNB and ALND groups were, 96.3% (95% CI, 92.2%–100%) and 94.2% (95% CI, 90.2%–98.5%) ( $p = 0.392$ ), respectively. In addition, the overall 5-year DFS rate was 87.6% (95% CI, 83.3%–92.1%); the corresponding rates for the SLNB and ALND groups were 89.2% (95% CI, 83.1%–95.8%) and 86.4% (95% CI, 80.6%–92.6%) ( $p = 0.671$ ), respectively (**Figure 1**).

In the Cox model, axillary surgery was not associated with OS or DFS (hazard ratio [HR], 1.900; 95% CI, 0.572–6.308 and HR, 0.863; 95% CI, 0.418–1.784, respectively). Clinical stage and tumor characteristics were not associated with OS or DFS (**Table 3**).

We performed a subgroup analysis by screening patients who were sentinel node-negative on SLNB. The characteristics of the subgroups are summarized in **Supplementary Table 1**. There was no significant difference in the OS (96.3% vs. 93.8%,  $p = 0.616$ ) and DFS rates (89.2% vs. 84.0%,  $p = 0.919$ ) between the two subgroups (**Supplementary Figure 1**). There was no difference in the recurrence rates between the two subgroups (**Supplementary Table 2**). All results were similar to those of the main study group.

### Complications

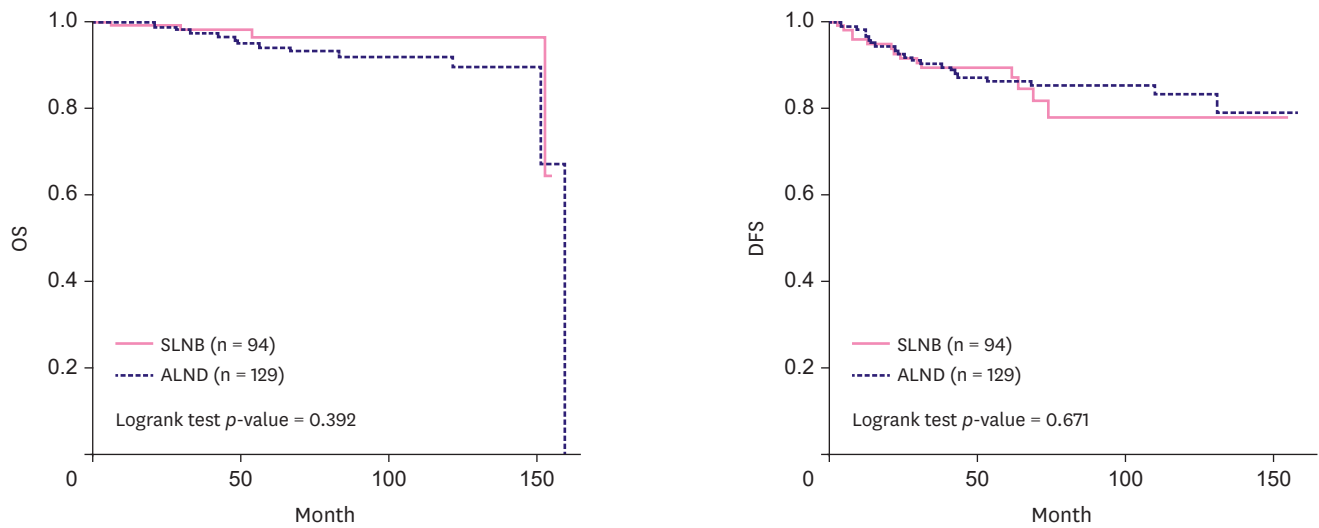
Complications occurred at a significantly higher rate in the ALND group than in the SLNB group (16.0% vs. 34.1%,  $p < 0.001$ ). Shoulder stiffness occurred in four and nine patients ( $p$

**Table 2.** Events in all patients after neoadjuvant chemotherapy

| Events                                      | Study group   |               |                | <i>p</i> -value |
|---|---------------|---------------|----------------|-----------------|
|   | All (n = 223) | SLNB (n = 94) | ALND (n = 129) |                 |
| <b>Recurrence</b>                           |               |               |                |                 |
| Loco-regional recurrence                    | 13 (5.8)      | 4 (4.3)       | 9 (7.0)        | 0.39            |
| Ipsilateral axillary lymph nodes recurrence | 4 (1.8)       | 1 (1.1)       | 3 (2.3)        | 0.48            |
| Distant metastasis                          | 21 (9.4)      | 10 (10.6)     | 11 (8.5)       | 0.59            |
| Total                                       | 34 (15.3)     | 14 (14.9)     | 20 (15.5)      | 0.90            |
| <b>Death</b>                                |               |               |                |                 |
| Death from breast cancer                    | 13 (5.8)      | 4 (4.3)       | 9 (7.0)        | 0.39            |
| Death from other causes                     | 3 (1.4)       | 0 (0.0)       | 3 (2.3)        | 0.14            |
| Total                                       | 16 (7.2)      | 4 (4.3)       | 12 (9.3)       | 0.15            |

Values are presented as number (%).

SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.



**Figure 1.** OS and DFS in the SLNB group and ALND group. OS = overall survival; DFS = disease-free survival; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

**Table 3.** Multivariate analysis of OS and DFS in the study group after adjusting for individual characteristics

| Prognostic factors              | Overall survival     |         | Disease free survival |         |
|---------------------------------|----------------------|---------|-----------------------|---------|
|                                 | HR (95% CI)          | p-value | HR (95% CI)           | p-value |
| <b>Axillary surgery</b>         |                      |         |                       |         |
| SLNB                            | 1.000                |         | 1.000                 |         |
| ALND                            | 1.900 (0.572–6.308)  | 0.294   | 0.863 (0.418–1.784)   | 0.69    |
| <b>Age</b>                      |                      |         |                       |         |
| < 40                            | 1.000                |         | 1.000                 |         |
| ≥ 40                            | 0.477 (0.156–1.460)  | 0.195   | 0.541 (0.261–1.125)   | 0.10    |
| <b>Initial clinical T stage</b> |                      |         |                       |         |
| T1–T2                           | 1.000                |         | 1.000                 |         |
| T3–T4                           | 0.990 (0.296–3.312)  | 0.987   | 1.994 (0.986–4.034)   | 0.06    |
| <b>Initial clinical N stage</b> |                      |         |                       |         |
| N1                              | 1.000                |         | 1.000                 |         |
| N2                              | 1.030 (0.289–3.672)  | 0.964   | 0.913 (0.406–2.050)   | 0.83    |
| N3                              | 1.318 (0.332–5.235)  | 0.695   | 1.216 (0.496–2.980)   | 0.67    |
| <b>Tumor subtype</b>            |                      |         |                       |         |
| HR+/HER2+                       | 1.000                |         | 1.000                 |         |
| HR+/HER2–                       | 0.547 (0.100–2.982)  | 0.486   | 0.324 (0.110–0.954)   | 0.04    |
| HR–/HER2+                       | 1.511 (0.225–10.147) | 0.671   | 0.615 (0.158–2.386)   | 0.48    |
| TNBC                            | 1.657 (0.392–6.999)  | 0.492   | 1.124 (0.457–2.762)   | 0.80    |

HR = hazard ratios; CI = confidence interval; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; HR+/- = hormone receptor-positive/-negative; HER2+/- = human epidermal growth factor receptor 2-positive/-negative; TNBC = triple negative breast cancer.

=0.57) in the SLNB and ALND groups, respectively. Arm lymphedema was the most common complication, and it was more common in the ALND group than in the SLNB group (8 [8.5%] vs. 35 [27.1%],  $p < 0.001$ ) (Table 4). Similar results were observed in the subgroups (Supplementary Table 3).

## DISCUSSION

This retrospective study of women who underwent neoadjuvant treatment for node-positive breast cancer showed that acceptable long-term locoregional control associated with the use of SLNB alone for women who converted to clinically node-negative (cN0) status after NAC



**Table 4.** Surgical complications

| Surgical complications | Study group   |               |                | p-value |
|------------------------|---------------|---------------|----------------|---------|
|                        | All (n = 223) | SLNB (n = 94) | ALND (n = 129) |         |
| Complication           |               |               |                | < 0.00  |
| Yes                    | 59 (26.5)     | 15 (16.0)     | 44 (34.1)      |         |
| No                     | 164 (73.5)    | 79 (84.0)     | 85 (65.9)      |         |
| Type of complications  |               |               |                |         |
| Arm lymphedema         | 43 (19.3)     | 8 (8.5)       | 35 (27.1)      | < 0.00  |
| Shoulder stiffness     | 13 (5.8)      | 4 (4.3)       | 9 (7.0)        | 0.57    |
| Seroma                 | 4 (1.8)       | 2 (2.1)       | 2 (1.6)        | 1.00    |
| Wound infection        | 1 (0.5)       | 1 (1.1)       | 0 (0.0)        | 0.42    |
| Bleeding               | 1 (0.5)       | 0 (0.0)       | 1 (0.8)        | 1.00    |

Values are presented as number (%).

SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

and achieved ypN0 status at the time of surgery. The primary findings of this study were that there was no significant difference in the OS and DFS rates between the SLNB and ALND groups during the median follow-up periods of 57 and 99 months, respectively. In addition, the locoregional recurrence rates, especially, ipsilateral axillary lymph node recurrence, were comparable across ypN0 patients regardless of the axillary surgery method.

Traditionally, ALND has been the standard treatment for axillary surgery after NAC in patients with node-positive breast cancer. In patients with clinically node-positive breast cancer who became cN0 after NAC, the use of SLNB instead of ALND was not recommended because of the high FNR (> 10%). There are concerns that potential residual axillary disease due to the high FNR may affect the likelihood of distant metastasis and survival. To address these concerns, several studies have assessed the long-term follow-up results of SLNB in such patients. Galimberti et al. [13] retrospectively assessed 396 patients with breast cancer with clinical T1-4 N0-2, who became or remained cN0 after NAC and underwent SLNB. In all cases, ALND was not performed if the sentinel lymph node was negative. After a median follow-up of 61 months, axillary recurrence occurred in only one patient (0.7%) among those who were initially N1/2 and became clinically N0. The long-term outcomes were similar for patients who were initially clinically N0 or N1/2. The authors concluded that SLNB is acceptable for patients with breast cancer converting from cN1/2 to cN0 after NAC. Kang et al. [14] analyzed 1,247 patients with breast cancer who had a clinical conversion of axillary lymph nodes from positive to negative following NAC during a median follow-up period of 48–51 months. Axillary and distant recurrence-free survival were not significantly different between the 428 and 819 patients in the SLNB and ALND groups, respectively. Wong et al. [15] reviewed 244 patients with clinical T1–3cN0–2 breast cancer who underwent NAC followed by SLNB for axillary staging. Of the 159 patients with ypN0 disease who underwent SLNB alone, the risk of local recurrence did not significantly differ between the cN0/ypN0 and cN1–2/ypN0 groups. Choi et al. [16] reviewed 506 patients with breast cancer with cytology-proven node metastasis who underwent NAC treatment followed by curative surgery. They classified patients into three groups: SLNB alone, SLNB+ALND, and ALND (ypN0). After a median follow-up of 51 months, there was no significant difference in axillary recurrence-free survival ( $p = 0.118$ ), DFS ( $p = 0.578$ ) or OS ( $p = 0.149$ ) among the three groups. As in previous studies, in this study, OS, DFS and ipsilateral axillary lymph node recurrence were not significantly different between the two groups, and subgroup analysis showed similar results (**Supplementary Figure 1, Supplementary Tables 2 and 3**). Our findings showed that there was no significant difference in outcome compared to that of the ALND group, despite the possibility of occult residual disease due to false negativity in the SLNB group, which supports the oncologic safety of SLNB alone in cN0/ypN0 patients after NAC.

However, a large multicenter prospective trial to validate these results is needed to define the criteria for axillary surgery in patients who have converted from lymph node-positive to clinically node-negative (cNO) status after NAC.

This study differs from previous studies in that only cNO/ypNO patients after NAC were selected to compare outcomes according to the axillary surgery method in a group of patients with a similar prognosis. Furthermore, multivariate analysis showed that OS and DFS were not significantly different regardless of the node status or tumor subtype (**Table 3**). This is thought to be because the ALND rate was relatively high in patients with advanced breast cancer, and only patients with axillary pCR (ypNO) after NAC were finally selected and compared. In contrast, Fernandez-Gonzalez et al. [17] showed that DFS and OS rates were higher in patients with ypNO disease (HR, 4.14; 95% CI, 2.03–8.43) than in ypN+ patients. According to the molecular-like subtype, the distant DFS and OS were also significantly different according to the pathologic status of the axilla after NAC (both,  $p < 0.001$ ).

The total median number of retrieved SLNs in our study (the median number of retrieved SLNs for a total of 165 patients, excluding 58 patients who immediately underwent ALND without identification of the sentinel node) was 2.3 (**Supplementary Table 4**), which was not sufficient to compensate for the high FNR in patients with neoadjuvant therapy. However, according to a recent study by Kahler-Ribeiro-Fontana et al. [18] the 10-year follow-up after removal of a median of two SLNs in cN1/2 patients who become cNO after NAC provides evidence that FNR does not lead to impaired clinical outcomes. These results provide evidence to support our findings.

Similar to the results of several previous studies [19–24], morbidity data favored the SLNB group, with a significantly lower incidence of arm lymphedema (8.5% vs. 27.1%) and shoulder stiffness (4.3% vs. 7.0%) noted in patients who underwent SLNB than in those who underwent ALND. Three patients in the ALND group experienced multiple complications (**Table 4**). Therefore, SLNB may be associated with relatively lower lymphedema and arm and shoulder morbidity likelihood than ALND after NAC.

This study had several limitations. First, since this study was retrospective in nature, there were no clear criteria for ALND and number of sentinel nodes to retrieve before surgery. Second, this was a single-center study with a small sample size; consequently, the incidence of ipsilateral axillary lymph node recurrence was low, precluding the evaluation of its association with other factors such as oncological factors other than surgery and radiation therapy. Third, to evaluate patient groups with similar prognoses, among patients who converted to cNO after NAC only data from patients who were ypNO were extracted and compared. Therefore, comparisons between patient groups with various prognoses are insufficient. Further prospective studies with a large population from multiple centers are needed to validate and complement our findings and define optimal axillary treatment recommendations.

In conclusion, our long-term follow-up results showed that ALND omission did not affect axillary lymph node recurrence or survival in patients who achieved an axillary complete response after NAC, supporting the current paradigm of de-escalation of axillary surgery following NAC [25].



## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Characteristics of the 165 patients with sentinel node-negativity proven by SLNB

[Click here to view](#)

### Supplementary Table 2

Events in subgroup after neoadjuvant chemotherapy

[Click here to view](#)

### Supplementary Table 3

Surgical complications in subgroup

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### Supplementary Table 4

Lymph node status of patients

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### Supplementary Figure 1

OS and DFS in the SLNB-alone subgroup and additional ALND subgroup.\*

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