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Original

Predictors of Pathologically Negative Sentinel Lymph Nodes and Recurrence-Free Survival in Women with Invasive Breast Cancer Treated with Neoadjuvant Chemotherapy

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Background: The accuracy and safety of sentinel lymph node (SLN) dissection (SLND) have not been established for women with invasive breast cancer (BC) who underwent neoadjuvant chemotherapy (NAC). The purpose of this study was to identify factors that predict pathologically negative axillary lymph node (ALN) status and recurrence-free survival (RFS) in women with invasive BC and clinically negative ALN after NAC followed by SLND.

Methods: The analysis included patients with BC (T1-4, N0-1, M0) treated with NAC who had clinically negative ALNs after NAC followed by SLND between January 2018 and May 2022. Age, clinical tumor size, clinical ALN status, estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2), molecular subtype, histological grade, Ki67, all at baseline, and pathologic tumor size after NAC were analyzed for correlations with pathological ALN metastasis and RFS.

Results: SLND identified at least one SLN (blue or radioactive node) in all of 112 consecutive patients. Multivariable analysis showed that age >50 years, clinically negative ALN, histologic grade II or III, ER negativity, triple negative subtype (all at baseline), and pathologically invasive tumor size of ≤2.0 cm after NAC showed a significant correlation with pathologically negative ALN. HER2 positivity and pathological complete response of the primary tumor were significantly correlated with favorable RFS.

Conclusions: These predictors of pathologically negative ALN and RFS after NAC are useful for planning appropriate surgical and adjuvant treatment for BC patients.

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Keywords: breast cancer, neoadjuvant chemotherapy, axillary lymph node, sentinel lymph node dissection, recurrence-free survival

Introduction

Breast cancer (BC) is the most common cancer worldwide and the leading cause of cancer death in women[1]. Axillary lymph node (ALN) dissection has a role in BC therapy but is associated with complications including numbness, paresthesia, and lymphedema, which limit

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daily activities[2,3]. Sentinel lymph node (SLN) dissection (SLND) reduces this morbidity and has become the standard of care for early BC with clinical ALN metastasis[4–9].

Neoadjuvant chemotherapy (NAC) is widely used in BC patients because it can increase the ratio of partial mastectomies to full mastectomies without increasing mortality[10]. Pathological complete response (pCR) after NAC predicts recurrence-free survival (RFS) and overall survival[11–16]. In addition, response-guided therapy, which can inform selection of an appropriate treatment based on the effect of NAC, has recently become common. As a result, the role of NAC has been expanded from the original indications of locally advanced or inflammatory BC to include early BC. The indications for NAC in operable BC include cases for which chemotherapy is necessary to improve survival and those for which partial mastectomy is preferred despite total mastectomy being recommended.

As mentioned above, SLND is used more frequently, even in patients who underwent NAC. However, identification rates of SLN and false-negative rates of SLND were worse in patients with clinically positive ALN metastasis before NAC, even when NAC was effective in converting positive ALN metastasis to negative[17,18]. Therefore, in clinically ALN-positive patients with an initial diagnosis of negative SLN metastasis after NAC, the effect of forgoing ALN dissection (ALND) has not been fully validated[19–22]. In contrast, dual SLND techniques using blue dye and radiocolloid and the removal of more than two ALNs, can increase SLN identification rates and lower false-negative rates[23–25].

Several studies reported that response to NAC varies in relation to BC molecular subtype. Human epidermal growth factor receptor 2 (HER2) and estrogen receptor (ER) are key factors that can define responsiveness to NAC. The HER2-positive and ER-negative (HER2-enriched) subtypes have the highest response rate, followed by the HER2-negative and ER-negative (triple negative, TN) subtype. The ER-positive (luminal) subtype shows the weakest response[26–29].

The aim of this study was to identify factors that predict pathologically negative ALN metastasis in patients with invasive BC treated with NAC followed by SLND and to identify predictors of RFS in these patients. The results of this study will provide valuable insights regarding when ALND is unnecessary after NAC and may even pave the way for omission of SLND after NAC in the future.

Patients and Methods

Patients

Data for this retrospective cohort study were collected by reviewing the electronic medical records of patients with primary invasive BC who underwent SLND after NAC in Nippon Medical School Hospital from January 2018 to May 2022. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Nippon Medical School Hospital Ethics Committee[30] (approval number: B-2022-511).

Inclusion criteria were invasive BC diagnosed by core needle biopsy with a clinical stage of cT1-4, cN0-1, M0, corresponding to stage I-IIIB disease. In addition, patients had to have received at least one cycle of NAC followed by SLND. At our center, N1 patients are eligible for SLND if they present with enlarged ALNs before treatment but have no pathologically confirmed metastasis and are clinically negative for metastasis after NAC. The presence of enlarged ALNs was determined using mammography, ultrasound, dynamic contrast-enhanced magnetic resonance imaging, and/or 5-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PETCT).

Exclusion criteria were recurrent BC, noninvasive BC, previous SLND in the same axilla, distant metastatic disease, and pathologically confirmed ALN metastasis.

The chemotherapy regimens were epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC), and/or taxanes, along with anti-HER2 antibodies such as trastuzumab alone or in combination with pertuzumab, which had been administered to patients with HER2-positive tumors.

Immunohistochemical Markers

HER2-positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or a score of 2+ confirmed by positive fluorescence in situ hybridization analysis, with a HER2/CEP17 ratio of ≥2.0. ER and PgR status were classified as positive or negative based on a threshold of ≥10% positively stained cells by IHC. The Ki67 labeling index was calculated as the average percentage of Ki67-positive cells across the entire tumor. Ki67 LI was classified as high if ≥20% and low if <20%. In this study, patients were divided into three BC subtypes. Tumors that were ER-positive and/or PgR-positive and HER2-negative were categorized as luminal HER2-negative subtype. All HER2-positive tumors were classified as HER2-positive subtype, irrespective of ER or PgR positivity. Tumors that were ER-negative, PgR-negative, and HER2-

negative were classified as the TN subtype.

SLNs and the Primary Tumor

Our SLND procedure was as follows. On the day before surgery Tc-99 m-phytate was injected beneath the areola, which was followed 2 to 3 hours later by SLN imaging of scintigraphy and hybrid single-photon emission computed tomography (SPECT)/computed tomography (CT) (SPECT/CT) imaging. On the day of surgery, a handheld gamma probe (Gamma Finder II™, Shilac Japan Co., Ltd., Osaka) was used to identify radioactive lymph nodes in the axilla after induction of anesthesia and before the start of surgery. Just before surgery, 1 mL of blue dye (Indigocarmine, Daiichi Sankyo, Japan) was injected subdermally into the areola, followed by gentle massage of the injection site for approximately 1 minute.

All radioactive nodes detected by gamma probe and/or all blue nodes were removed. A radioactive node was defined as one with radioactivity of 10% or more compared with the highest radioactivity. Non-blue, non-radioactive nodes suspected of metastasis and those simultaneously removed during SLND were also included in the SLN category. All excised SLNs were examined ex-vivo using the gamma probe to record the level of radioactivity. Nodes were classified as a blue radioactive node, radioactive-only node, blue-only node, or non-blue, non-radioactive node. All these SLNs were immediately sent to the hospital pathology department for intraoperative histological examination of frozen sections.

If the SLNs showed evidence of macrometastasis (maximum diameter >2 mm), further ALND was routinely performed. However, if SLNs were tumor-free, contained isolated tumor cells (ITCs) (maximum diameter ≤0.2 mm), or exhibited micrometastasis (maximum diameter ≤2 mm), ALND was not usually carried out. The final pathological diagnosis of ALNs was categorized as absence (ypN0) or presence (ypN+) of ALN metastasis. The latter category included ITCs (ypN0(i+)), micrometastasis (ypN1mi), and macrometastasis (ypN1a, 2a, 3a). Pathological tumor size after NAC was classified as ypT0, ypTis, and ypT1-4. In this study, pCR of the primary tumor was defined as ypT0 and ypTis.

Survival Statistics

RFS was investigated by using Kaplan-Meier analysis of clinical and pathological factors. In addition, clinical and pathological characteristics of patients with recurrence were analyzed in detail.

Clinical and Pathological Factors

Age, clinical tumor size, clinical ALN status, ER, PgR, HER2, molecular subtype, histological grade, Ki67 LI, all at baseline, and pathologically invasive tumor size after NAC were analyzed for correlations with pathological ALN metastasis and RFS.

Statistical Methods

Descriptive statistics of patient characteristics are presented as frequencies and percentages. Univariable and multivariable analysis of patient characteristics and pathological nodal status were performed using risk regression analysis. All variables were included in the univariable analysis. Significant variables from the univariable analysis were included in the multivariable analysis, along with other factors potentially influencing outcomes, including age, tumor size, nodal status, and histological grade. This analysis was performed using STATA® 15. A p value of <0.05 was considered to indicate statistical significance.

Results

We analyzed data from 112 consecutive BC patients with cT1-4, cN0-1, M0 (stages I to III) cancer treated with NAC followed by SLND between January 2018 and May 2022. **Table 1** shows the baseline clinical and pathological characteristics of the cohort in relation to ypN status. The median age of the patients was 53 years (range: 30 to 81 years). Most patients (103, 91.9%) had cT1 and cT2 tumors. Fourteen patients (12.5%) were classified as having cN1 disease, although none had cytologically confirmed ALN metastasis. All clinically ALN-positive cases converted to clinically ALN-negative after NAC. Regarding tumor subtypes, 44 patients (39.3%) had luminal HER2-negative tumors, 41 (36.6%) had HER2-positive tumors, and 27 (24.1%) had TN tumors. Eighty-five patients (75.9%) had tumors with a high Ki67 LI score (≥20%).

Table 2 shows the NAC regimen, number of removed SLNs, surgery type, and pathological tumor size (ypT) after NAC in relation to pathological nodal metastasis (ypN). Sixty-five patients (58.1.%) received an EC or AC with or without taxanes. Among the 42 patients with HER2-positive tumors, 38 (90.5%) received anti-HER2 antibodies in combination with NAC, while the remaining 4 patients (9.5%) received HER2 antibodies as part of adjuvant therapy.

Primary tumor pCR (pathological complete response; ypT0 or ypTis) was achieved in 40 patients (35.7%) (**Table 2**). The pCR rate was highest in HER2-positive tu-

Table 1 Baseline clinical and pathological characteristics, by pathological ALN metastasis

Variables	All N=112	ypN0 n=100 (89.3%)	ypN+ n=12 (10.7%)	p value
Age (years)				0.35
≤50	47 (42.0%)	40 (85.1%)	7 (14.9%)	
>50	65 (58.0%)	60 (92.3%)	5 (7.7%)	
cT stage				0.21
T1	38 (33.9%)	36 (94.7%)	2 (5.3%)	
T2	65 (58.0%)	57 (87.7%)	8 (12.3%)	
T3	7 (6.3%)	5 (71.4%)	2 (28.6%)	
T4	2 (1.8%)	2 (100.0%)	0 (0.0%)	
cN stage				0.17
N0	98 (87.5%)	89 (90.8%)	9 (9.2%)	
N1	14 (12.5%)	11 (78.6%)	3 (21.4%)	
Histological type				1.0
IDC	110 (98.2%)	98 (89.1%)	12 (10.9%)	
ILC	2 (1.8%)	2 (100.0%)	0 (0.0%)	
Histological grade				0.20
1	16 (14.2%)	12 (75.0%)	4 (25.0%)	
2	57 (50.4%)	51 (89.5%)	5 (10.5%)	
3	32 (28.3%)	30 (93.6%)	2 (6.4%)	
Unknown	8 (7.1%)	7 (87.5%)	1 (12.5%)	
ER				0.004
Negative	54 (48.2%)	53 (98.1%)	1 (1.9%)	
Positive	58 (51.8%)	47 (81.0)	11 (19.0)	
PgR				0.22
Negative	38 (33.9%)	36 (94.7%)	2 (5.3%)	
Positive	74 (66.1%)	64 (86.5%)	10 (13.5%)	
HER2				0.029
Negative	70 (62.5%)	59 (84.3%)	11 (15.7%)	
Positive	42 (37.5%)	41 (97.6%)	1 (2.4%)	
Subtype				0.005
Luminal HER2-negative	43 (38.4%)	33 (76.7%)	10 (23.3%)	
HER2-positive	42 (37.5%)	41 (97.6%)	1 (2.4%)	
TN	27 (24.1%)	26 (96.3%)	1 (3.7%)	
Ki67 LI				0.40
Low (<20%)	22 (19.6%)	18 (81.8%)	4 (18.2%)	
High (≥20%)	85 (75.9%)	77 (90.6%)	8 (9.4%)	
Unknown	5 (4.5%)	5 (100.0%)	0 (0.0%)	

ALN, axillary lymph node; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; PgR, progesterone receptor; TN, triple-negative; cT, clinical T; cN, clinical N; ypN+ includes ypN0 (i+) ypN1mi, ypN1a, ypN2a, and ypN3a.

mors (29 of 42 patients, 69.1%), followed by TN tumors (5 of 27 patients, 18.5%) and luminal HER2-negative tumors (6 of 43 patients, 14.0%) (data not shown in table).

At least one SLN (blue or hot node) was identified from SLND in all 112 patients, an identification rate of 100%. The identification rate would have decreased to 99% (111 of 112) with the use of radiocolloid alone and to 89% (100 of 112) with blue dye alone. Among the 112 patients, 12 (11%) had metastatic SLNs. Specifically, macrometastasis was observed in nine patients, micrometastasis in one patient, and ITCs were identified in two patients.

Incident node-negative status after NAC (ypN0) was observed in 100 cases (89.3%) (**Tables 1 and 2**). No sig-

Table 2 Treatment-related clinical and pathological characteristics, by pathological ALN metastasis

Variables	All N=112	ypN0 n=100	ypN+ n=12	p value
NAC				0.033
EC or AC+/-T	66 (58.9%)	56 (84.9%)	10 (15.2%)	
T or TC	8 (7.14%)	6 (75.0%)	2 (25.0%)	
EC or AC +T+ T-mab+/-P-mab	30 (26.8%)	30 (100.0%)	0 (0.0%)	
T or TC + T-mab+/-P-mab	8 (7.14%)	8 (100.0%)	0 (0.0%)	
No. of Removed SLNs				0.11
1–2 nodes	77 (68.8%)	69 (89.6%)	8 (10.4%)	
3–4 nodes	30 (26.8%)	28 (93.3%)	2 (6.7%)	
≥5 nodes	5 (4.5%)	3 (60.0%)	2 (40.0%)	
Axillary surgery				<0.001
SLND	104 (92.9%)	100 (96.2%)	4 (3.8%)	
ALND	8 (7.1%)	0 (0.0%)	8 (100.0%)	
Breast surgery				0.76
Total mastectomy	62 (55.4%)	56 (90.3%)	6 (9.7%)	
Partial mastectomy	50 (44.6%)	44 (88.0%)	6 (12.0%)	
ypT				<0.001
T0 / Tis	40 (35.7%)	40 (100.0%)	0 (0.0%)	
T1	60 (53.6%)	54 (90.0%)	6 (10.0%)	
T2	12 (10.7%)	6 (50.0%)	6 (50.0%)	

AC, doxorubicin and cyclophosphamide; ALN, axillary lymph node; ALND, axillary lymph node dissection; EC, epirubicin and cyclophosphamide; NAC, neoadjuvant chemotherapy; SLN, sentinel lymph node; SLND, sentinel lymph node dissection; TC, docetaxel and cyclophosphamide; T-mab, trastuzumab; P-mab, pertuzumab; ypN+ includes ypN0 (i+), ypN1mi, ypN1a, ypN2a, and ypN3a.

nificant correlation was found between age, cT, cN, histological type, histological grade, PgR, Ki67 LI, and ypN0 on the chi-square test (**Table 1**).

Among the 54 ER-negative cases, ypN0 status was achieved in 53 (98.1%) cases, as compared with 47 of 58 ER-positive cases (81.0%) (p=0.004) (**Table 1**). Similarly, ypN0 status was achieved in 41 of 42 HER2-positive cases (97.6%) and in 59 of 70 HER2-negative cases (84.3%) (p=0.029) (**Table 1**).

Regarding subtype, the incidence of ypN0 significantly differed between the luminal HER2-negative, HER2-positive, and TN subtypes (p=0.006) (**Table 1**). In HER2-positive subtype cases, ypN0 was achieved in 97.6%, as previously described. In 27 TN subtype cases, 26 (96.3%) achieved ypN0. In 43 luminal HER2-negative subtype cases, 33 (76.7%) achieved ypN0. The incidence of ypN0 for the luminal HER2-negative subtype was significantly lower than for the HER2-positive and TN subtypes.

Among the 14 cases with cN1 status, 11 (78.6%) were ypN0 after NAC, compared to 89 (90.8%) of 98 cases with cN0 status. However, this difference was not significant (**Table 1**). Of the 11 cN1 cases that converted to ypN0, six were HER2-positive, three were TN, and two were luminal HER2-negative subtype cases (data not shown). In contrast, among the nine cN0 patients diagnosed with ypN+ after NAC, eight were identified as having luminal HER2-negative subtype tumors, while one had a HER2-positive tumor (data not shown).

Regarding NAC regimens analyzed in relation to ypN0, ypN0 was achieved in all 38 cases treated with anti-HER2 antibodies (p=0.033) (**Table 2**). Regarding pathological tumor size after NAC (ypT) in relation to ypN0, all 40 cases of both ypT0 and ypTis (100%) were ypN0, 54 of 60 cases of ypT1 (90%) were ypN0, and six of 12 cases of ypT2 (50%) were ypN0 (p<0.001) (**Table 2**).

The results of multivariable analysis of factors that predict ypN0 are shown in **Table 3**. Incidence of ypN0 was significantly positively correlated with age older than 50 years (vs ≤50 years), cN0 (vs cN1), histological grade 2 or 3 tumors (vs grade 1 tumors), ER-negative tumors (vs ER-positive tumors), TN tumors (vs luminal or HER2-positive tumors), and ypT0, Tis, or T1 tumors (vs ypT2) (**Table 3**).

Among the 12 SLN-positive patients, four did not receive ALND (**Table 2**) and all had only one positive SLN. Two of these patients with SLN macrometastasis underwent breast-conserving surgery followed by radiation therapy to the breast and axilla, one with ITCs under-

Table 3 Multivariable analysis for predictors of ypN0

	Multivariable analysis		
Variables	Risk ratio for ypN0	95% CI	p value
Age			
≤50	1		
>50	1.14	1.01–1.27	0.029
NAC			
EC or AC+/-T	1		
T or TC	0.8	0.59–1.08	0.14
EC or AC +T+ T-mab+/-P-mab	1.62	0.65–4.66	0.29
T or TC + T-mab+/-P-mab	1.77	0.72–4.38	0.22
cT			
T1	1		
T2	0.94	0.85–1.04	0.26
T3	0.51	0.24–1.09	0.086
T4	1.75	0.65–4.66	0.26
cN			
N0	1		
N1	0.76	0.59–0.99	0.041
Histological grade			
1	1		
2	1.32	1.02–1.72	0.033
3	1.48	1.11–1.97	0.006
No. of removed SLNs			
1–2 nodes	1		
3–4 nodes	1.01	0.91–1.12	0.813
≥5 nodes	0.96	0.67–1.38	0.841
ER			
Negative	1		
Positive	0.84	0.72–0.97	0.018
PgR			
Negative	1		
Positive	1.11	0.94–1.31	0.21
HER2			
Negative	1		
Positive	0.66	0.26–1.62	0.36
Subtype			
Luminal HER2-negative	1		
HER2-positive	0.75	0.28–1.99	0.561
TN	1.15	1.00–1.32	0.042
Ki67 LI			
Low (<20%)	1		
High (≥20%)	0.84	0.69–1.02	0.075
ypT			
T0 / Tis	1		
T1	1	0.92–1.10	0.85
T2	0.51	0.30–0.87	0.013

AC, doxorubicin and cyclophosphamide; CI, confidence interval; cT, clinical T; cN, clinical N; EC, epirubicin and cyclophosphamide; T-mab, trastuzumab; P-mab, pertuzumab; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; PgR, progesterone receptor; SLN, sentinel lymph node; TC, docetaxel and cyclophosphamide; TN, triple-negative.

went total mastectomy with no postoperative radiation therapy, and one was later diagnosed as having SLN macrometastasis, using permanent sections after surgery, and later underwent radiation therapy to the chest wall, axilla, and supraclavicular areas.

After a median follow up of 24 months, four patients developed recurrence. The characteristics of these four recurrent cases are shown in **Table 4**. Time to recurrence ranged from 15 to 26 months. Two cases were luminal HER2-negative subtype and two were TN subtype. Total mastectomy or nipple sparing mastectomy with SLND alone was performed in all four cases. pCR was not achieved in any of these patients. Case #1 received post-mastectomy radiation therapy because of the presence of macrometastasis in the SLN, which was postoperatively diagnosed using permanent sections. Case #4 developed a recurrence in regional LNs despite being confirmed as ypN0 by SLND. Of the 100 patients with ypN0, one (1%) developed recurrence in the axilla.

In Kaplan-Meier survival analysis, RFS did not differ in relation to breast tumor subtype (**Figure 1**). However, RFS was significantly longer for patients with HER2-positive tumors than for those with HER2-negative tumors (p=0.04) (**Figure 2**). In addition, RFS was significantly longer for patients who achieved pCR (ypT0 or ypTis, and ypN0) than for those who did not (p=0.024).

Discussion

Previous studies reported that axillary pCR was achieved in 30% to 55% of clinically node-positive patients after NAC[16,31,32]. These results suggest that when NAC is effective and ALNs are negative on imaging, SLND can be performed and ALND is unnecessary when the result of SLND is negative. However, this treatment strategy is not the standard of care, because false-negative rates of SLND after NAC are higher than when no NAC performed[20,32,33] and safety has not been confirmed. In addition, SLN identification rates are reported to be lower after NAC.

A dual SLND technique can improve the SLN identification rate and decrease the rate of false-negatives[24,31]. The present SLN identification rate was 100%, exceeding the 93.8% rate reported in the ACOSOG Z1071 trial[32], perhaps because of the use of the dual method (blue dye and radiocolloid). However, the higher success rate in this study may result from the larger number of cN0 cases before NAC. This is supported by the findings of a meta-analysis of patients initially classified as cN0, which reported an SLN identification rate of 96%[33], higher than

Table 4 Characteristics of four cases with recurrence

Case No.	Age (years), cT cN	Subtype	NAC	Clinical response	Surg. method	ypN	ypT	Adjuvant therapy	Rec. sites	Time to rec. (mo.)
#1	50, T1 N0	Luminal HER2-negative	EC+T	PR	TM SLND	1a	1	Radiation, Tam	Bone	18
#2	54, T2 N0	Luminal HER2-negative	EC+T	SD	NSM SLND	0	1	Ana	Skin (local)	15
#3	69, T2 N0	TN	EC+T	SD	TM SLND	0	2	None	Lung, Brain	25
#4	71, T2 N0	TN	EC+T	PR	TM SLND	0	1	None	Liver, ALN	26

ALN, axillary lymph node; Ana, anastrozole; EC, epirubicin and cyclophosphamide; NAC, neoadjuvant chemotherapy; No., number; NSM, nipple-sparing mastectomy; PR, partial response; Rec., recurrence; SD, stable disease; SLND, sentinel lymph node dissection; Surg., Surgery; T, taxanes; TM, total mastectomy; Tam, tamoxifen; TN, triple negative.

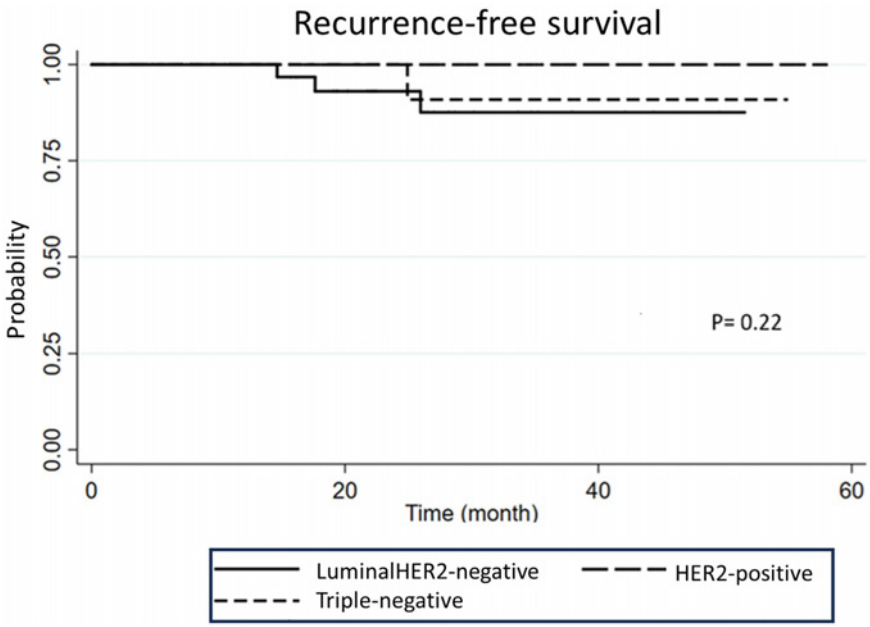

Figure 1 Kaplan-Meier plot of recurrence-free survival (RFS) in relation to breast cancer subtype
There was no significant difference in RFS between breast cancer subtypes.
RFS: Recurrence-free survival; HER2: Human epidermal growth factor receptor 2.

that reported in the ACOSOG Z1071 trial. Another reason for the present high identification rate from SLN may be the use of preoperative lymphoscintigraphy and additional SPECT/CT imaging. SPECT/CT provides valuable additional information on SLNs, including anatomical location, size, and shape, which facilitates accurate SLND[34,35]. However, SPECT/CT is only available in a limited number of hospitals in Japan.

Given the tendency for SLN identification rates to decrease after NAC, a more important focus is identifying patients who are more likely to achieve ypN0 status after NAC, thus potentially avoiding unnecessary axillary surgery. Several studies have assessed factors that predict ypN0 after NAC, with the aim of identifying patients suitable for sparing axillary surgery.

The present univariable analysis revealed that the TN and HER2-positive subtypes were more likely the luminal HER2-negative subtype to be ypN0. This finding is consistent with previous studies[20,36–41]. Other factors that predicted ypN0 at baseline were cN0, higher histological grade (2 or 3), ER negativity, and lower residual tumor burden (ypT0, ypTis or ypT1). Some of these findings are consistent with the results of a Dutch study, which reported that the strongest predictors of ypN0 after NAC were tumor subtype and tumor grade at baseline and breast radiological CR on MRI[20]. In the present study, although tumor response on MRI after NAC was not analyzed, ypT0 or ypTis being predictive for ypN0 might

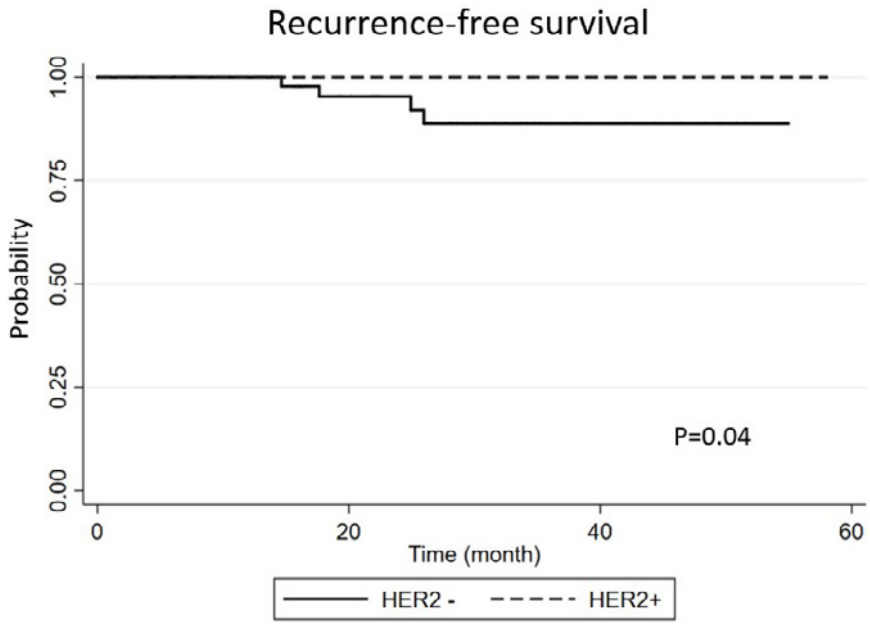

Figure 2 Kaplan-Meier plot of recurrence-free survival (RFS) in relation to HER2 expression
Patients with HER2-positive tumors had significantly better RFS than did those with HER2-negative tumors (p=0.04).
RFS: Recurrence-free survival; HER2-: Human epidermal growth factor receptor 2 negative; HER2+: Human epidermal growth factor receptor 2 positive.

correlate with radiological CR on MRI.

In our study, patients older than 50 years had a higher incidence of ypN0, which is consistent with the findings of a Chinese study[37] that reported that a higher Ki67 labeling index was a significant predictor of ypN0, a correlation not observed in our analysis. However, our study had a smaller sample size (N=112 vs N=350). Additionally, our study predominantly included patients with clinically node-negative disease, whereas the Chinese study included patients with clinically node-positive disease. These differences may explain the discrepancies in the results.

Previous studies reported that the HER2-enriched subtype was the strongest predictor factor for ypN0, followed by the TN and luminal subtypes[28,37,41,42]. Although our findings indicate that ER-negative status and HER2-positive status both predicted ypN0 in univariable analysis, only ER-negative status remained a significant predictor after adjustment for multiple variables. In our study, the HER2-positive category included both ER-negative and ER-positive cases; however, in previous studies, the HER2-enriched subtype was defined as HER2-positive and ER-negative. This HER2-enriched subtype was not analyzed independently in our study because of the small number of such cases. Thus, the results of our multivariable analysis of HER2 positivity should not be overly emphasized. However, HER2 positivity remains undeniably important in predicting ypN0.

There is debate as to whether ER-negativity or HER2-positivity is the stronger predictor of ypN0. In our multivariate analysis, HER2 positivity was not an independent predictor, possibly because of the inclusion of ER-positive cases, as mentioned above. In addition, our result may be attributable to the larger number of cN0 patients (87% of all patients in the study). Whereas in other studies, most patients were clinically node-positive before NAC. In reviewing other cN0 studies, we found similarities between our results and those reported by van der Noordaa et al.[20]. They reported that the TN subtype was the strongest predictive factor for ypN0 and that for the TN subtype, breast pCR did not further contribute to the prediction of nodal disease, a finding consistent with our result that almost all TN cases were ypN0, even if the breast was not pCR.

A study of a US national cancer database of clinically node-positive patients who had received NAC reported that SLND alone was performed in more than 10% of patients with ypN+ disease[43]. Among the ypN+ patients receiving SLND alone, 13% had ypN1, 35% had ITCs, and 50% had undergone breast-conserving surgery. Similarly, in our study, 33% of ypN+ patients did not receive ALND, because of factors such as smaller metastatic foci

and postoperative radiation therapy.

In our survival analysis, all patients with HER2-positive tumors remained relapse-free, demonstrating a significantly higher survival rate in comparison to patients with HER2-negative tumors. Previously, HER2-positivity was associated with poor prognosis. However, development of HER2-targeted therapies such as the anti-HER2 monoclonal antibodies trastuzumab and pertuzumab has substantially improved outcomes. Recently, response-guided therapy has been introduced after NAC. For non-pCR cases after NAC, T-DM1 is prescribed for HER2-positive breast cancer[44] and capecitabine for HER2-negative breast cancer[45], resulting in improved survival rates for breast cancer patients across all subtypes. However, previous studies[46,47] clearly show that patients who achieve pCR after NAC have significantly better survival rates, which is consistent with the present findings.

The main limitation of this study is its relatively small sample size, particularly of patients who were clinically node-positive before neoadjuvant chemotherapy. In addition, the median follow-up duration of 24 months is relatively short for evaluating RFS, especially for luminal subtypes that are prone to late recurrence. Although only four recurrences were observed—two in triple-negative and two in luminal subtypes—this low event rate may partly reflect the short follow-up and may underestimate the true recurrence risk. Furthermore, the external validity of our findings is limited, particularly in patients with cN1 disease who converted to clinically node-negative status after NAC. Therefore, our results should be interpreted with caution, and it is premature to suggest omission of SLND after NAC. Larger prospective studies with longer follow-up and careful patient selection are warranted before drawing firm conclusions about oncologic safety.

Conclusions

In this study dual-modality SLND yielded a high identification rate (100%) of SLN even after NAC in patients with clinically node-negative or suspected node-positive BC. ER negativity and HER2 positivity are significant predictors of ypN0. Other factors predicting ypN0 included older age, higher histological grade and clinical node negativity at baseline, and smaller pathological tumor size after NAC. HER2 positivity and achievement of pCR in the breast and axilla significantly improved RFS after NAC.

These predictors of pathologically negative ALN and RFS after NAC may help guide planning of surgical and adjuvant treatments for breast cancer patients. However, because of the small sample size, short follow-up duration, and limited recurrence events, our findings should be interpreted with caution. While the results provide useful insights into situations where ALND after NAC might be omitted, the suggestion to omit SLND remains premature. Larger and longer prospective studies are needed before we can draw firm conclusions regarding the oncologic safety of omitting SLND after NAC.

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