Original Study



# The Loss of Lymph Node Metastases After Neoadjuvant Chemotherapy in Patients With Cytology-proven Axillary Node-positive Primary Breast Cancer

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## Abstract

**Axillary lymph node dissection after neoadjuvant chemotherapy still remains a standard treatment of patients with breast cancer with LN metastases before neoadjuvant chemotherapy. Our results showed that 3 or more residual lymph node metastases after NAC were rare in patients with LN metastases before neoadjuvant chemotherapy with estrogen receptor-negative/human epidermal growth factor receptor 2-positive or estrogen receptor-negative/human epidermal growth factor receptor 2-negative tumors who were assessed as clinically lymph node-negative after neoadjuvant chemotherapy by ultrasonography. It indicated that no complete axillary lymph node dissection might be needed for these populations.**

**Background:** Axillary lymph node (LN) dissection after neoadjuvant chemotherapy (NAC) still remains a standard treatment of initially LN-positive primary breast cancer because of the difficulty of assessment of LN status. The aim of this study was to assess the LN status after NAC in initially LN-positive primary breast cancer patients who were assessed as clinically LN-negative after NAC (ycN0) and identify factors associated with loss of LN metastasis. **Patients and Methods:** The study cohort comprised 279 patients with cytology-proven LN-positivity before NAC. LN status was assessed by ultrasonography. Regional recurrence-free survival and overall survival according to pathologic LN after NAC (ypN) status were assessed in patients with ycN0. **Results:** Of the 279 patients, 179 patients (64.2%) had ycN0. High nuclear grade, estrogen receptor-negative ($ER^-$), and human epidermal growth factor receptor 2-positive ($HER2^+$), were significant predictors of ycN0/ypN0 ($P < .001$, .007, and .046, respectively). Metastases persisted in 1 or 2 LNs for 5 (20.0%) of 25 patients with $ER^-/HER2^+$ and for 4 (21.1%) of 19 patients with $ER^-/HER2^-$, and in 3 or more LNs for 0 (0%) of 25 patients with $ER^-/HER2^+$ and for 1 (5.3%) of 19 patients with $ER^-/HER2^-$. Patients with $ER^+$ tumors had more numerous residual LN metastases than those with $ER^-$ tumors ($P < .001$). Among patients with ycN0, ypN status was not associated with regional recurrence-free survival or overall survival. **Conclusions:** Three or more residual LN metastases were rare in patients with $ER^-$ tumors if assessed as ycN0 by ultrasonography. Prospective studies are needed to confirm the prognostic impact of not performing axillary lymph node dissection in such patients.

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## Introduction

Neoadjuvant chemotherapy (NAC) is one of the standard therapies for operable invasive breast cancer.[1,2] Over 30% of patients with breast cancer and axillary lymph node (LN) metastases reportedly achieve axillary pathologic complete response (pCR) after NAC,[3-9] whereas the rate of response to NAC depends on breast cancer subtype.[10,11] However, assessment of LN status after NAC by physical examination or ultrasonography (US) is problematic because of the high false-negative rate (FNR) of over 40%.[12-14] The FNR by sentinel lymph node biopsy (SNB) after NAC is also over 10%.[13-16] Therefore, axillary LN dissection (ALND) remains a standard treatment of patients with LN metastases before NAC (cN+).[17] However, ALND has a high rate of complications, including lymphedema, sensory loss, and motor weakness.[18] Furthermore, recent regimens for NAC, especially those incorporating a human epidermal growth factor receptor-2 (HER2)−targeting agent for HER2-positive ($HER2^+$) breast cancer, have significantly improved pCR rates.[19-23] The ability to accurately predict the loss of LN metastases would make omission of ALND safe in selected patients. We therefore sought to assess the pathologic LN status after NAC in initially LN-positive patients with primary breast cancer who were assessed as clinically LN-negative after NAC (ycN0), and to identify the factors associated with the loss of LN metastases after NAC in patients with cN+ primary breast cancer. We also assessed the prognosis of patients who achieved ycN0 according to pathologic LN status.

## Patients and Methods

### *Patients*

From 997 consecutive patients who had undergone surgery after NAC from January 2006 to December 2016, 279 with cytology-proven LN metastases before NAC were included in this retrospective study. Patients with clinical T4 tumors, supra/subclavicular and parasternal LN metastases, and distant metastases were excluded.

Clinicopathologic factors, including age, nuclear grade (NG), clinical tumor size (cT), estrogen receptor (ER) status, HER2 status, LN status before and after NAC (clinical N before NAC: cN, clinical N after NAC: ycN, and pathologic N after NAC: ypN), and number of pathologically proven residual axillary LN metastases, were analyzed. The need for written informed consent was waived by the Institutional Review Board because of the retrospective nature of this study. All specimens were collected in accordance with a protocol approved by the Institutional Review Board.

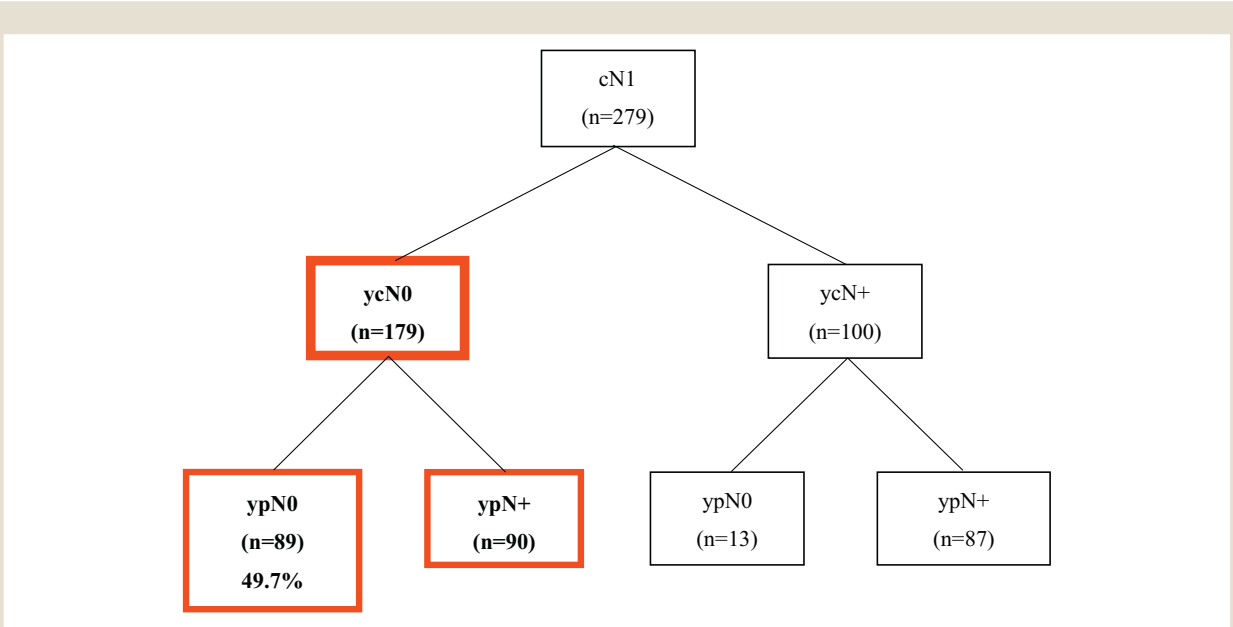
### *Radiologic Assessment of Axillary LN*

All patients were assessed by computed tomography (CT) or positron emission tomography (PET-CT) scan before NAC to assess the presence of distant metastasis. US examinations were performed for assess LN status before and after NAC using color Doppler US equipment (mainly HI VISION Preirus; Hitachi Medical, Chiba, Japan). cN+ was confirmed by fine-needle aspiration cytology if LN metastases were suspected on the basis of US findings of reduced fatty deposition and lateral cortical hypertrophy.[13] The axilla ipsilateral to the breast cancer was assessed by 2 board-certified radiologists (H.T.) with > 15 years of experience in breast US, using a 10-L linear probe with a frequency range of 5 to 12 MHz. All patients underwent high-resolution gray scale US (B-mode) of the ipsilateral axilla to determine the morphologic features of their LN.

### *Pathologic Examination*

Surgically excised LNs were cut into slices (thickness, 2 mm) and fixed in 10% neutral-buffered formalin to prepare paraffin blocks.

**Figure 1** Ultrasonography Findings in Axillary Nodes After Neoadjuvant Chemotherapy and Their Accuracy. Eighty-Nine of 179 ycN0 Patients (49.7%) had ypN0, While 13 of 100 ycN+ Patients (13.0%) had ypN0




Abbreviations: ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy; ycN+ = clinically lymph node-positive after neoadjuvant chemotherapy; ypN0 = pathologically lymph node-negative after neoadjuvant chemotherapy; ypN+ = pathologically lymph node-positive after neoadjuvant chemotherapy.

**Table 1** Patients' Clinicopathologic Characteristics According to Axillary Lymph Node Status

| | All n | ycN0 n (%) | ypN0/ycN0 n (%) | ypN+/ycN0 n (%) |
|---|---|---|---|---|
| No. patients | 279 | 179 (64.2) | 89 (49.7) | 90 (50.3) |
| Median age, y (range) | 48 (23-75) | 51 (23-75) | 49 (28-73) | 46 (23-73) |
| cT | | | | |
| 1 | 58 | 43 (74.1) | 22 (51.2) | 21 (48.8) |
| 2 | 187 | 116 (62.0) | 56 (48.3) | 60 (51.7) |
| 3 | 34 | 20 (58.8) | 11 (55.0) | 9 (45.0) |
| NG | | | | |
| 1 | 99 | 60 (60.6) | 17 (28.3) | 43 (71.7) |
| 2 | 91 | 56 (61.5) | 27 (48.2) | 29 (51.8) |
| 3 | 89 | 63 (70.8) | 45 (71.4) | 18 (28.6) |
| ER | | | | |
| Positive | 217 | 135 (62.2) | 55 (40.7) | 80 (59.3) |
| Negative | 62 | 44 (71.0) | 34 (77.3) | 10 (22.7) |
| HER2 | | | | |
| Positive | 80 | 64 (80.0) | 41 (64.1) | 23 (35.9) |
| Negative | 199 | 115 (57.8) | 48 (41.7) | 67 (58.3) |
| Histology | | | | |
| IDC | 268 | 172 (64.2) | 87 (50.6) | 85 (31.7) |
| Others | 11 | 7 (63.6) | 2 (28.6) | 5 (71.4) |
| Regimen | | | | |
| Anthracycline + taxane | 265 | 174 (65.7) | 89 (51.1) | 85 (48.9) |
| Others | 14 | 5 (35.7) | 0 (0) | 5 (100) |
| Trastuzumab-containing regimen | 47 | 38 (80.9) | 28 (73.7) | 10 (26.3) |

Abbreviations: cT = clinical tumor stage; ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; IDC = invasive ductal carcinoma; NG = nuclear grade; ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy; ypN0 = pathologically lymph node-negative after neoadjuvant chemotherapy; ypN+ = pathologically lymph node-positive after neoadjuvant chemotherapy.

Several slides (thickness; 2 mm) were cut from each block and stained with hematoxylin and eosin and immunohistochemical stains (cytokeratins AE1/AE3) for evaluation. The LN specimens were then assessed by breast pathologists with > 20 years of experience (K.S.). Biomarkers on the primary tumors were determined using biopsy samples obtained before chemotherapy, baseline ER and progesterone receptor (PR) expression being assessed by immunohistochemistry (IHC) and scored by the Allred method, with Allred scores of 3 or greater being considered positive. $HER2^+$ was defined as HER2 3+ by IHC, or HER2 2+ and HER2 gene amplification shown by fluorescence in situ hybridization (cutoff value of HER2 to CEP17: 2.0).[24,25] After pathologic examination, LN status after NAC was categorized into 2 categories: ypN0 or ypN+. Isolated tumor cells (ITCs) were included in ypN0, and micrometastasis was defined as node-positive. The number of LN with micrometastasis or ITCs were not assessed.

### *Statistical Analysis*

Logistic regression was used to identify factors associated with ypN0 in patients with ycN0. Odds ratios with 95% confidence intervals (CIs) were calculated. The Mann-Whitney *U* test was performed for associations between ER status and number of residual axillary LN metastases in patients with ycN0. Regional recurrence-free survival (RRFS) and overall survival (OS) by ypN status in patients with ycN0 were compared using the log-rank test. Duration of RRFS was defined as days from the date of surgery to the date of diagnosis of regional LN recurrence and duration of OS from the date of surgery to the date of death, or last follow-up. $P < .05$ was considered to denote significance.

## Results

### *Clinicopathologic Factors Associated With ypN0 in Patients With ycN0*

Axillary LN status after NAC was ycN0 in 179 (64.2%) of the 279 patients with cytology-proven LN metastases before NAC. The

**Table 2** ycN0 and ypN0 According to Breast Cancer Subtype

| Subtype | ycN0 N | ypN0/ycN0 n (%) | ypN+/ycN0 n (%) |
|---|---|---|---|
| $ER^+/HER^-$ | 96 | 34 (35.4) | 62 (64.6) |
| $ER^+/HER^+$ | 39 | 21 (53.8) | 18 (46.2) |
| $ER^-/HER^-$ | 19 | 14 (73.7) | 5 (26.3) |
| $ER^-/HER^+$ | 25 | 20 (80.0) | 5 (20.0) |
| Total | 179 | 89 (49.7) | 90 (50.3) |

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy; ypN0 = pathologically lymph node-negative after neoadjuvant chemotherapy; ypN+ = pathologically lymph node-positive after neoadjuvant chemotherapy.

**Table 3** Univariate and Multivariate Analysis of Clinicopathologic Variables Associated With Pathologic Nodal Status in Patients With ycN0

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Age (<50 y vs. ≥ 50) | 0.59 | 0.31-1.12 | .084 | 0.86 | 0.43-1.69 | .653 |
| cT (1 vs. 2, 3) | 1.08 | 0.51-2.27 | .828 | – | – | – |
| NG (3 vs. 1,2) | 4.09 | 2.01-8.44 | < .001 | 3.61 | 1.79-7.29 | < .001 |
| ER (negative vs. positive) | 4.95 | 2.15-12.08 | < .001 | 3.18 | 1.37-7.38 | .007 |
| HER2 (positive vs. negative) | 2.49 | 1.27-4.93 | .004 | 2.07 | 1.01-4.22 | .046 |
| Histology (IDC vs. others) | 2.56 | 0.40-27.42 | .254 | – | – | – |

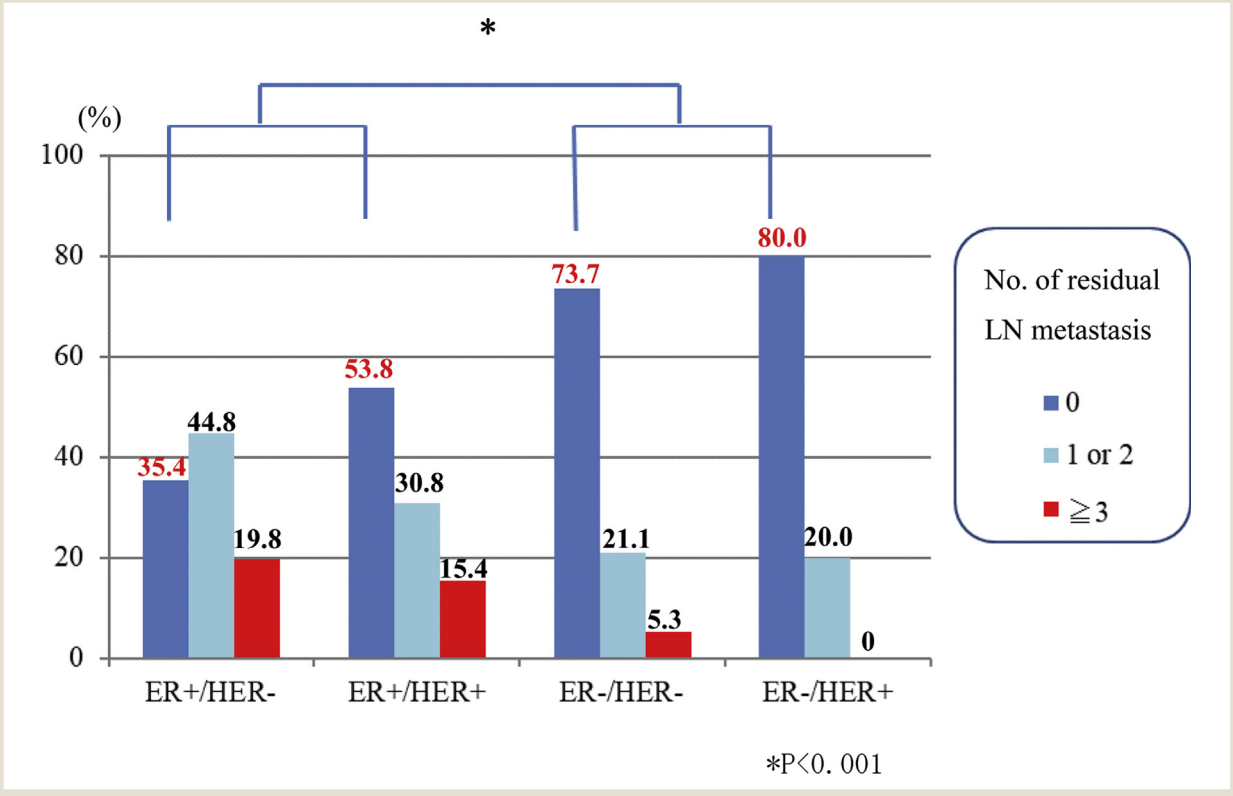
Abbreviations: cT = clinical tumor stage; ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; IDC = invasive ductal carcinoma; NG = nuclear grade; OR = odds ratio; ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy.

number of ypN0 in patients with ycN0 was 89 (49.7%) of the 179 (Figure 1). Patients' characteristics are summarized in Table 1. The rate of ypN0 in patients with ycN0 by each subtype was 80.0% with $ER^-/HER2^+$ tumors, 73.7% with $ER^-/HER2^-$ tumors, 53.8% with $ER^+/HER2^+$ tumors, and 35.4% with $ER^+/HER2^-$ tumor (Table 2). The clinicopathologic factors associated with ypN0 in patients with ycN0 are shown in Table 3. According to univariate analysis, NG 3, $ER^-$, and $HER2^+$ were significantly associated with ypN0 in patients with ycN0 ($P < .001$, $P < .001$, and $P = .004$, respectively). In multivariate analysis, all 3 of these factors were also independent predictors of ypN0 in patients with ycN0 ($P < .001$, $P = .007$, and $P = .046$, respectively).

### *The Number of Residual Axillary LN Metastasis*

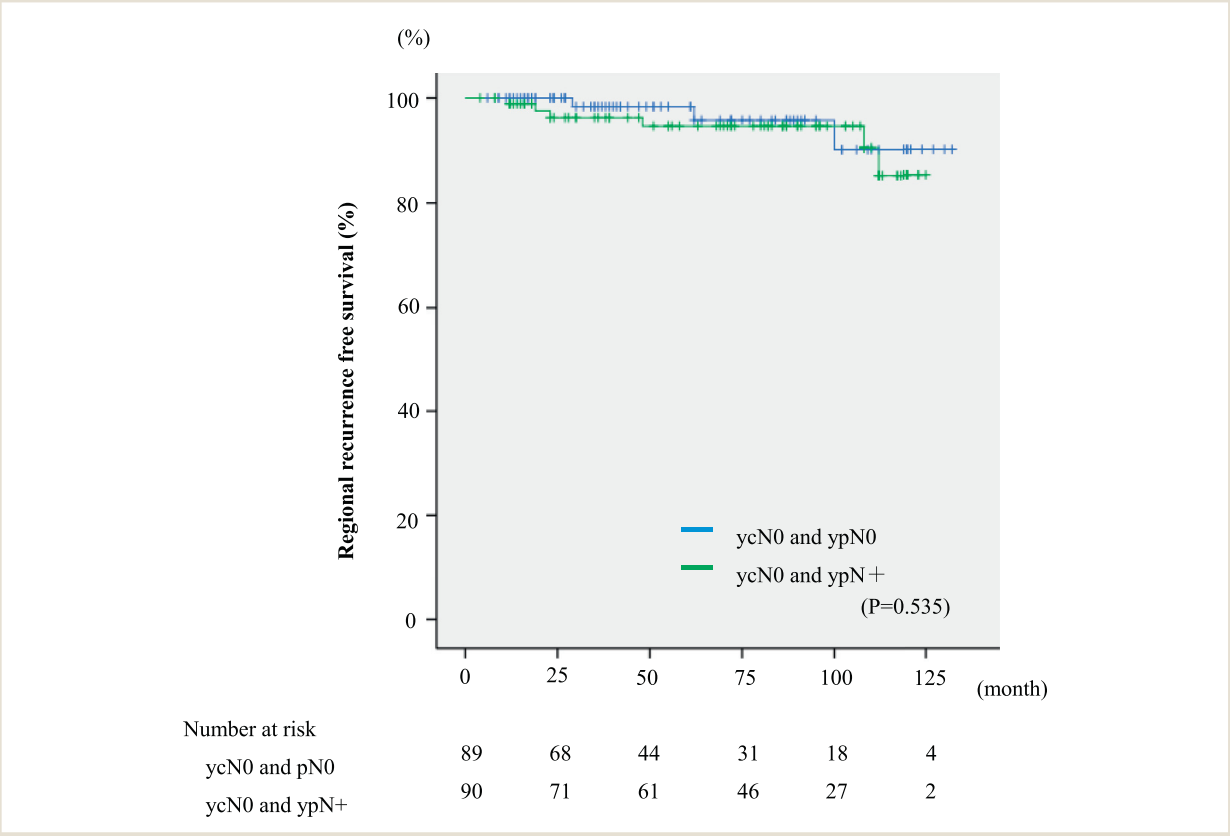
Ninety (50.3%) of the 179 patients with ycN0 had residual LN metastasis after NAC. Metastases persisted in 1 or 2 LNs for 5

**Figure 2** The Number of Residual Axillary LN Metastasis in Patients With ycN0




Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; LN = lymph node; ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy.

**Figure 3** Regional Recurrence-free Survival According to Pathologic Lymph Node Status in Patients With ycN0




Abbreviation: ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy.

(20.0%) of 25 patients with $ER^-/HER2^+$ tumors, for 4 (21.1%) of 19 with $ER^-/HER2^-$ tumors, 12 (30.8%) of 39 with $ER^+/HER2^+$ tumors, and 43 (44.8%) of 96 with $ER^+/HER2^-$ tumors (Figure 2). However, 3 or more LN metastases remained in 0 (0%) of 25 patients with $ER^-/HER2^+$ tumors, 1 (5.3%) of 19 with $ER^-/HER2^-$ tumors, 6 (15.4%) of 39 with $ER^+/HER2^+$ tumors, and 19 (19.8%) of 96 with $ER^+/HER2^-$ tumors (Figure 2). Patients with $ER^+$ tumors had significantly more numerous residual LN metastases than those with $ER^-$ tumors ($P < .001$).

### *RRFS and OS of Patients With ycN0 Status According to ypN Status*

With the median follow-up period of 69 months, RRFS did not differ between those with ypN0 and ypN+ among the patients with ycN0 ($P = .535$) (Figure 3). Also, there was no difference in OS between ypN0 and ypN+ in these patients with ycN0 ($P = .792$) (Figure 4).

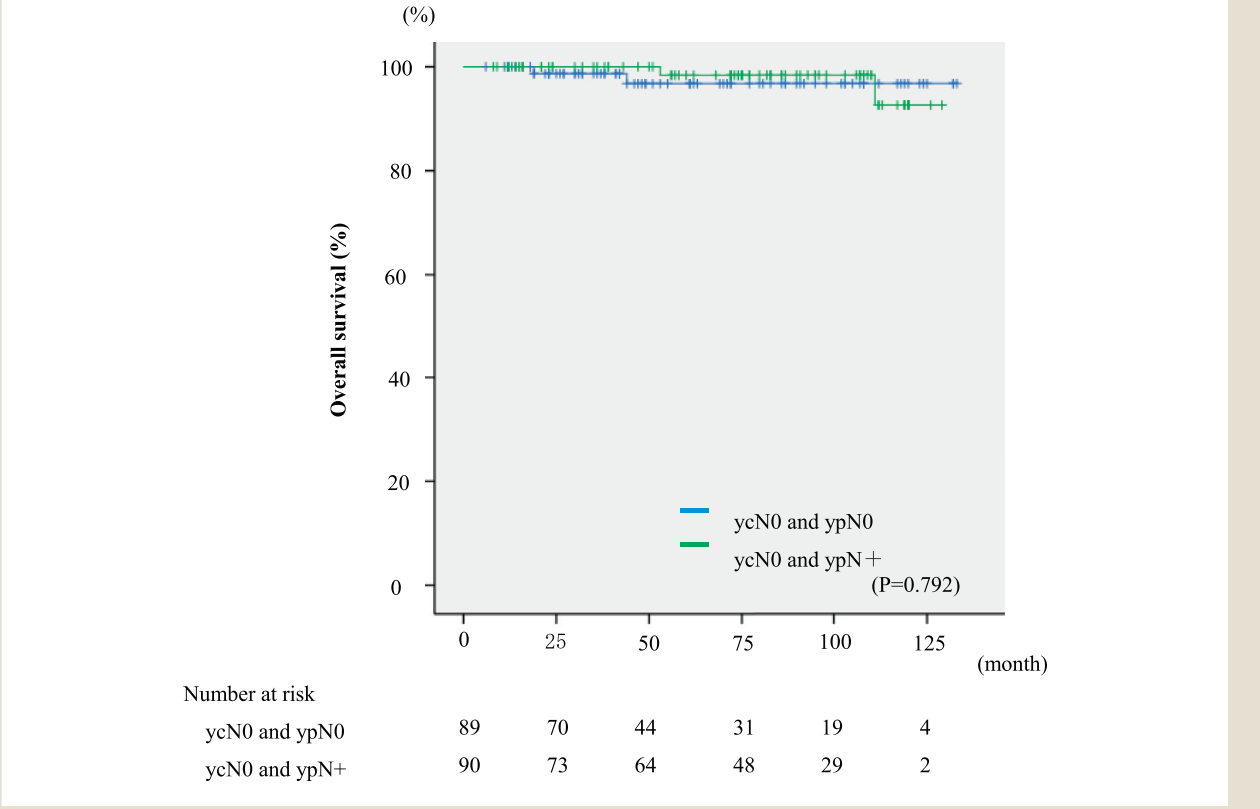
### *The Association Between PR Status and ypN0/ycN0 or the Number of Residual LN Metastasis*

In $ER^+/HER2^-$ tumors, the rate of ypN0/ycN0 was 62.5% in the $PR^-$ group, and 29.1% in the $PR^+$ group ($P = .011$). The percentage of patients with 3 or more residual LN metastases after NAC was 12.5% in $ER^+/PR^-$ tumors, whereas it was 21.3% in $ER^+/PR^+$ tumors.

## Discussion

Our study showed that a high percentage of patients with initially cytology-proven LN-positive primary breast cancer with $ER^-/HER2^+$ and $ER^-/HER2^-$ tumors did not have residual LN metastases if assessed as ycN0 after NAC by US. In addition, even if LN metastases remained, 3 or more LN metastases were very rarely shown for these populations. Furthermore, the prognosis of patients with ycN0 did not differ according to ypN status. These results indicated that complete ALND might not be necessary in patients with ycN0 and $ER^-/HER2^+$ or $ER^-/HER2^-$ tumors. In contrast, patients with $ER^+$ tumors had a high risk of residual LN metastases after NAC, even if assessed as ycN0. Although PR-positivity might affect the number of residual LN metastasis in $ER^+$ tumors, the accuracy of ycN0 is still not enough. Therefore, ALND is still a standard treatment for patients with cN+ and $ER^+$ tumors before NAC. Several studies have determined whether SNB could be safely substituted for complete ALND after NAC.[3,5-9,13-16,26] In terms of accuracy of ycN0, In the ACOSOG Z1071 (Alliance) trial, 159 (47.6%) of 334 patients with ycN0 were SNB-positive without considering breast cancer subtype.[15] Our results showed that the

**Figure 4** Overall Survival According to Pathologic Lymph Node Status in Patients With ycN0




Abbreviations: ycN0 = clinically lymph node-negative after neoadjuvant chemotherapy; ypN0 = pathologically lymph node-negative after neoadjuvant chemotherapy; ypN+ = pathologically lymph node-positive after neoadjuvant chemotherapy.

accuracy of ycN status after NAC as determined by US depends on ER and HER2 status. In our previous prospective study, the FNR of SNB after NAC was 3.2% for $ER^-/HER2^+$ tumors but 16.0% for the whole study cohort.[26] However, these results also suggested that 20.5% of patients with ycN0 and $ER^-/HER2^+$ tumors and 31% of those with $ER^-/HER2^-$ tumors might need ALND because the SNB was positive or not identified. In the ACOSOG Z1071 trial, the FNR for SNB was 31.5% for only 1 sentinel LN (SLN) and 12.6% for 2 or more SLNs.[15] The SENTINA study (The accuracy of sentinel-lymph-node biopsy in patients with breast cancer before annd after neoadjuvant chemotherapy) reported a FNR of SNB for 14.2% of patients with ycN0 as determined by physical examination and US findings.[16] These results suggested that SNB could not safely be substituted for ALND because of the high FNR of > 10% of SNB after NAC. Some previous studies have proposed that assessment of the loss of LN metastases after NAC by a combination of SNB and US reduced the FNR. Using the ACOSOG Z1071 trial's algorithm, Boughey et al showed a reduction of FNR from 12.6% to 9.8%.[27]

To our knowledge, no previous studies have assessed number of residual LN metastases according to breast cancer subtype in patients with ycN0. From our results of the low risk of residual LN metastases after NAC, SNB with small number of LN sampling, instead of complete ALND, for patients with initial LN metastases and ycN0 may be enough for $ER^-/HER2^+$ tumors or $ER^-/HER2^-$ tumors.

One technique to identify the initially positive LNs for reducing the FNR of SNB is targeted axillary dissection (TAD), which includes SNB and selective localization and removal of clipped nodes.[28-30] Alternatively, the results of the AMAROS trial (Comparison of complete axillary lymph node dissection with axillary radiation therapy in treating women with invasive breast cancer trial [ClinicalTrials.gov, number NCT00014612]) reported the prognostic impact of postoperative radiation therapy for SLN-positive patients.[31] Thus, further prospective studies are needed to assess whether radiation therapy could substitute for axillary surgical treatment after NAC for patients with cN+ and ycN0.

In our previous study, we have shown that the prognostic impact of change in tumor size and LN status after NAC depends on subtype. From the results, tumor downstaging and loss of node positivity after NAC improved prognosis, regardless of non-pCR in patients with hormone receptor-positive/$HER2^-$/high nuclear grade or hormone receptor-negative/$HER2^-$ tumors. In contrast, in patients with $HER2^+$ tumors, only achievement of pCR was a prognostic factor.[32] In the current study, we found that ypN status did not affect prognosis in patients assessed as having ycN0. This may be attributable to the fact that all patients had undergone ALND. However, 80 of 90 patients who were ypN+/ycN0 were

also $ER^+$. As shown in Figure 2, the rate of 3 or more residual LN metastases was less than 19.8% of ycN0 patients. Furthermore, the total number of events was small with relatively short follow-up period for these populations. These factors with small residual tumor burden might be affect these results of no prognostic difference between ypN0 and ypN+ in ycN0 patients. All residual LN metastases should be treated to improve prognosis by a less invasive axillary procedure, avoiding the severe complications associated with ALND.

The CTNeoBC pooled analysis (The relationship between pathological complete response and long-term clinical benefit in breast cancer) revealed the strong association of pCR rate with prognosis for patients who received chemotherapy with trastuzumab in $HER2^+$ breast cancer.[33] It suggested that pCR might be associated with prognosis among patients with the same background and treatment. The Neosphere trial showed that the addition of pertuzumab to trastuzumab with chemotherapy increased pCR rate, and pCR had better prognosis than that of non-pCR.[34] These results indicated that a higher pCR rate would improve the accuracy of ycN0 and increase an opportunity to avoid no complete axillary dissection.

This study had some limitations. First, these data were retrospectively collected in a single institute. Second, it is difficult to accurately assess the number of initial LN metastases before NAC on the basis radiologic findings. The original number of LN metastases before NAC might be associated with the number of residual LNs. However, it is difficult to assess the exact number of LN metastases by US or CT. Therefore, the number of LN metastases were not included in this analysis. Third, the Ki 67 level, which would be helpful to classify luminal B-like tumors, was not included in this analysis because of no measurement in a large number of patients during this study period. We are conducting a multicenter prospective study to confirm our findings and assess the prognostic impact of alternative procedures, including LN sampling or radiation therapy in addition to SNB for patients with ycN0 and $ER^-/HER2^-$ and $ER^-/HER2^+$ tumors.

## Conclusion

We have shown that high-grade, $ER^-$, and $HER2^+$ are independent predictors of ypN0 in patients with ycN0. Furthermore, 3 or more residual LN metastases after NAC in patients with $ER^-/HER2^+$ and $ER^-/HER2^-$ tumors who assessed as ycN0 by US were rare. Prospective studies are warranted to confirm the prognostic impact of not performing complete ALND in such patients.

### *Clinical Practice Points*

- ALND after NAC still remains a standard treatment of initially LN-positive primary breast cancer because of the difficulty of assessment of LN status. However, over 30% of patients with breast cancer and axillary LN metastases reportedly achieve axillary pCR after NAC.
- We showed that high grade, $ER^-$, and $HER2^+$ are independent predictors of ypN0 in patients with ycN0 after NAC. Furthermore, 3 or more residual LN metastases after NAC in patients with $ER^-/HER2^+$ (0%) and $ER^-/HER2^-$ (5.3%) tumors were rare in patients assessed as ycN0 by US. We also showed that, among patients with ycN0, ypN status was not associated with RRFS and OS.
- These results indicated that complete ALND might not be necessary in $ER^-/HER2^+$ or $ER^-/HER2^-$ tumors in patients with initially LN-positive primary breast cancer if assessed as ycN0 after NAC by US.

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## Disclosure

The authors have stated that they have no conflicts of interest.

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