J Breast Cancer. 2025 Dec;28(6):437-447
https://doi.org/10.4048/jbc.2025.0157
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Study Protocol

A Randomized Trial of Sentinel Node Biopsy Omission After Neoadjuvant Systemic Therapy in Clinically Node-Negative or Selected Node-Positive Breast Cancer

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Received: Jun 30, 2025
Revised: Aug 21, 2025
Accepted: Oct 20, 2025
Published online: Nov 14, 2025

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ABSTRACT

Purpose: Axillary surgery is increasingly omitted in patients with early-stage breast cancer undergoing upfront surgery, as supported by trials such as SOUND and INSEMA. However, in the neoadjuvant setting, the omission of axillary surgery has only been explored in small single-arm studies involving highly selected patients with confirmed breast pathologic complete response (pCR). The NeoNAUTILUS trial aimed to evaluate the oncologic safety of omitting sentinel lymph node biopsy (SLNB) in patients with a high probability of achieving an axillary pCR (ypN0) following neoadjuvant systemic therapy (NST), regardless of breast pCR status.

Methods: NeoNAUTILUS is a prospective, multicenter, randomized, controlled, non-inferiority trial conducted at 12 tertiary centers in Korea. Eligible participants were women with clinical T1–T3, N0, or selected N1 invasive breast cancer, who completed NST and were candidates for breast-conserving surgery (BCS). Prior to enrollment, all patients underwent

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Trial Registration
ClinicalTrials.gov Identifier: NCT06704945. Registered on November 26, 2024.
Clinical Research Information Service Identifier: KCT0010174. Registered on February 7, 2025.

Funding
This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, South Korea (grant number: RS-2025-02243044). The grant source had no role in the design, preparation, or conduct of the study, including the collection, management, analysis, and interpretation of data.

Conflict of Interest
Wonshik Han reports serving as a member of the board of directors and holding stock and ownership interests in DCGen Co., Ltd., outside the submitted work. The other authors declare that they have no competing interests.

Data Availability
In accordance with the ICMJE data-sharing policy, the authors agree to make the data available upon request.

Author Contributions
Conceptualization: Jung JJ, Han W; Funding acquisition: Jung JJ, Han W; Investigation: Kim HJ, Chae BJ, Kim E, Ahn JH, Jeong J, Lee S, Jung SP, Woo J, Min J, Cheun JH, Chung MS, Shin KH, Chang JM, Moon WK; Methodology: Jung JJ, Shin KH, Chang JM, Moon WK, Han W; Project administration: Han W; Supervision:

axillary ultrasound after NST completion to exclude suspicious lymph nodes. Patients with clinical N0 disease of any subtype were eligible for inclusion. Patients with clinical N1 disease with human epidermal growth factor receptor 2-positive or triple-negative tumors may be included if their primary tumor demonstrates a > 30% reduction on magnetic resonance imaging after NST. Participants were randomized 1:1 to undergo BCS with or without SLNB, stratified by clinical nodal status and tumor subtype. Patients were randomized and remained blinded until surgery. The primary endpoint is the 5-year invasive disease-free survival. A total of 464 patients are expected to be enrolled over 3 years, with a 5-year follow-up period.
Discussion: NeoNAUTILUS is the first randomized trial to assess the omission of axillary surgery after NST based on the predicted nodal response, independent of breast pCR. This study may redefine axillary management in the neoadjuvant setting by identifying patients who can safely avoid SLNB, thereby reducing surgical morbidity without compromising oncologic outcomes.

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Keywords: Breast Neoplasms; Clinical Trial; Multicenter Study; Neoadjuvant Therapy; Sentinel Lymph Node Biopsy

INTRODUCTION

Axillary surgery is increasingly omitted in patients with early-stage breast cancer who undergo upfront surgery [1]. The Sentinel node vs Observation after axillary UltraSouND trial (SOUND; NCT02167490) was the first prospective study to demonstrate that sentinel lymph node biopsy (SLNB) provides no recurrence or survival benefit compared with no axillary surgery in patients with invasive tumors less than 2 cm and negative preoperative axillary ultrasound who undergo breast-conserving surgery (BCS) followed by adjuvant radiotherapy [2]. The Intergroup Sentinel Mamma trial further confirmed the non-inferiority of SLNB omission in patients with tumors measuring up to 5 cm (INSEMA; NCT02466737) [3]. Two additional trials are ongoing: The Dutch Breast Cancer Research Group 2013-08 (BOOG 2013-08; NCT02271828) [4] and the No Axillary Surgical Treatment for Lymph Node–Negative Patients after Ultrasonography (NAUTILUS; NCT04303715) [5], both of which are evaluating the omission of SLNB in clinically node-negative patients undergoing BCS. The results of these studies are expected to be reported within the next few years.

Reflecting this shift, the focus has turned toward omitting axillary surgery after neoadjuvant systemic therapy (NST) in carefully selected populations expected to have no metastatic nodal disease in the final pathology (ypN0). Accurate patient selection is essential for the success of these approaches, and two ongoing European trials, The European Breast Cancer Research Association of Surgical Trialists-01 (EUBREAST-01; NCT04101851) and Avoiding Sentinel Lymph Node Biopsy in Breast Cancer Patients After Neoadjuvant Chemotherapy (ASICS; NCT04225858), have limited the inclusion criteria to clinically node-negative patients with confirmed breast pathologic complete response (pCR), particularly in triple-negative breast cancer (TNBC) or the human epidermal growth factor receptor 2 (HER2)-positive subtype, as the nodal positivity rate was less than 2% in these patients [6]. The Avoidance of Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy (ASLAN; NCT04993625) trial, which was the first to complete accrual, broadened eligibility to include

Han W; Writing - original draft: Jung JJ; Writing - review & editing: Ahn JH, Chang JM, Moon WK, Han W.

cN1 disease and estrogen receptor (ER)-low-positive tumors, with primary endpoint analysis anticipated in the near future [7]. More recently, the Omission of Breast Surgery for Breast Cancer Patients With pCR on magnetic resonance imaging (MRI) and Vacuum-assisted Biopsy After NST trial (OPTIMIST; NCT05505357) investigated the safety of omitting axillary surgery in selected patients with confirmed breast pCR via vacuum-assisted biopsy [8]. In these patients, the entire surgical procedure after NST was omitted.

Nonetheless, all the aforementioned trials require confirmed breast pCR, and axillary surgery is necessary when residual disease is present in the breast, even if the axilla is expected to be tumor-free. To investigate whether omitting axillary surgery can be safely applied to patients expected to achieve ypN0 regardless of breast pCR, we conducted a retrospective study demonstrating that the majority of selected patients achieved axillary pCR (95.2%) despite only 46.1% achieving breast pCR, and they showed excellent oncologic outcomes [9]. These findings provide an evidence-based rationale for designing the first prospective trial titled "A Randomized Trial of Sentinel Node Biopsy Omission After Neoadjuvant Systemic Therapy in Clinically Node-Negative or Selected Node-Positive Breast Cancer (NeoNAUTILUS)," to validate the omission of axillary surgery after NST using criteria predictive of axillary pCR.

METHODS

Study design

The NeoNAUTILUS trial is a prospective, multicenter, randomized controlled trial conducted at 12 tertiary care hospitals in South Korea (**Supplementary Table 1**). Additional sites may be added as needed to ensure adequate participant enrollment. This study aims to evaluate the oncologic safety of omitting SLNB in patients predicted to achieve ypN0 after NST.

Eligible participants are women aged 20 years or older with clinical T1–T3, N0, or selected N1 invasive breast cancer who have completed NST and are candidates for BCS. The selection of cN1 patients is based on predictive criteria from the model by Kim et al. [10] and is further supported by our prior retrospective validation study [9]. Before enrollment, all patients underwent axillary ultrasound to assess the post-NST nodal status and exclude any suspicious lymph nodes. After providing written informed consent, the participants were randomized in a 1:1 ratio to undergo BCS with SLNB (SLNB group) or BCS without axillary surgery (no-SLNB group). Randomization is stratified based on clinical N stage and tumor subtype, and patients remained blinded to the group allocation until surgery.

The planned study duration is 8 years, comprising 3 years for patient accrual and 5 years for follow-up (**Figure 1**). A total of 464 patients are expected to be enrolled in this study. Recruitment began on May 19, 2025, and the first patient was enrolled on June 5, 2025. Enrollment is expected to be completed by May 2028.

Ethical statement

The design and conduct of this trial follow the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines, ensuring adherence to internationally recognized standards for clinical trial protocols. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H-2410-138-1581), with the initial approval granted on December 6, 2024. The current version of the protocol (version 2.0) was approved on June 18, 2025. Informed consent is obtained in person by an

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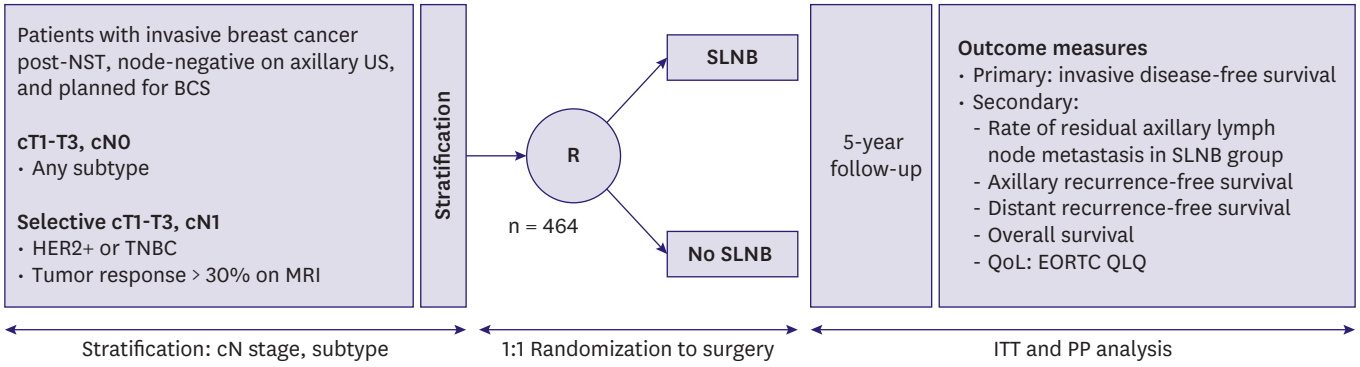

Figure 1. Study design.
Proposed randomized trial evaluating the of omission axillary surgery after NST based on axillary response rather than breast pCR. Eligible patients included those with cT1-T3 and cN0 breast cancer of any subtype and selected cN1 patients with a favorable axillary response. Patients were randomized to undergo BCS with or without SLNB, with 5-year invasive disease-free survival as the primary endpoint.
NST = neoadjuvant systemic therapy; pCR = pathologic complete response; BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy; US = ultrasound; cT = clinical tumor stage; cN = clinical node stage; HER2+ = human epidermal growth factor receptor 2-positive; TNBC = triple-negative breast cancer; MRI = magnetic resonance imaging; QoL = quality of life; EORTC QLQ = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; ITT = intention-to-treat; PP = per-protocol.

appropriately designated investigator or trained research coordinator at each participating institution before initiating any study-specific procedures.

This trial is registered at ClinicalTrials.gov (NCT06704945) and the Clinical Research Information Service of Korea (KCT0010174). Any modifications to the protocol beyond the current version will require agreement among all investigators and approval from the IRB. All changes will be updated promptly in the trial registries.

Study population

Participants were screened for eligibility based on predefined inclusion and exclusion criteria. The inclusion criteria were as follows: women aged 20 years or older with pathologically confirmed invasive breast cancer; no clinical or radiological evidence of distant metastasis; clinical T1–T3, N0 disease regardless of subtype or imaging response; selected clinical T1–T3, N1 disease with HER2-positive tumor (regardless of hormone receptor status); triple-negative (ER-negative, progesterone receptor-negative, and HER2-negative), or ER-low-positive (defined as ER expression of 1%–10% by immunohistochemistry or an Allred proportion score of 2) subtypes; and more than a 30% tumor size reduction on post-NST MRI. Breast MRI at the completion of NST was required only for patients who were initially cN1. For patients with cN0 disease at presentation, MRI was not mandatory for eligibility, regardless of the tumor subtype.

All patients underwent axillary ultrasound to assess post-NST lymph node status, and the presence of any suspicious lymph nodes was an exclusion criterion [11]. Ultrasound images were interpreted by a board-certified radiologist at each participating institution. If a single lymph node met any of the predefined suspicious criteria listed in **Table 1**, the patient was excluded. Additional inclusion criteria included completion of at least half of the originally planned NST cycles, regardless of dose reduction, an Eastern Cooperative Oncology Group performance status of 0–2, and the ability to understand and provide written informed consent.

https://doi.org/10.4048/jbc.2025.0157

Table 1. Ultrasound-based exclusion criteria for suspicious axillary lymph nodes following neoadjuvant systemic therapy

Suspicious findings for axillary lymph node metastasis after NST
‣ Cortical thickness greater than or equal to 2.5 mm
‣ Asymmetric cortical thickening or eccentric cortical bulging
‣ Hypoechoic, round-shaped lymph node
‣ Partial or complete loss of fatty hilum
‣ Extracapsular extension of the lymph node
‣ Intranodal microcalcifications

NST = neoadjuvant systemic therapy.

Patients were excluded if they had a history of any cancer within the past 5 years (excluding adequately treated non-melanoma skin cancer and *in situ* carcinoma other than breast carcinoma *in situ*), bilateral or inflammatory breast cancer, contraindications to radiotherapy, lymph node metastasis outside the axilla, a planned mastectomy, current pregnancy or breastfeeding, inability to complete study questionnaires, or concurrent participation in another clinical trial involving a surgical intervention.

Screening and randomization

All participants underwent screening assessments to confirm eligibility based on predefined inclusion and exclusion criteria. The screening procedures were initiated after obtaining written informed consent. These procedures included medical history taking, physical examination, breast and axillary ultrasound, and pregnancy testing (if indicated). Additional diagnostic tests were performed at the discretion of the investigator when clinically indicated. If eligibility was confirmed, patients were enrolled and randomized via a web-based platform managed by the Medical Research Collaborating Center at Seoul National University Hospital. Randomization was performed in a 1:1 ratio using a stratified block design, with stratification based on the clinical N stage and tumor subtype. The randomization table was generated using the SAS software (version 9.4; SAS Institute Inc., Cary, USA), and access to the system was restricted to authorized investigators. During randomization, investigators were required to input protocol-specific information, including trial number, site name, screening number, clinical N stage, and tumor subtype. A unique randomization number was assigned and recorded in all subject-related documentation. Participants remained blinded to their assigned treatment arms until the day of surgery to reduce potential bias or dropouts. This randomization procedure was adapted from the NAUTILUS protocol with minor modifications to reflect the updated design of the NeoNAUTILUS study.

Interventions and follow up

The patients underwent surgery as assigned, either BCS with or without SLNB. In the SLNB group, additional axillary dissection was performed based on SLNB results at the discretion of the investigator and in accordance with each institution's treatment policies. After surgery, all patients received standard adjuvant therapy, including systemic treatment and radiotherapy, as clinically indicated. The details of the radiotherapy protocol are described in a separate section.

Patients will be followed-up for at least 5 years after surgery, with additional surveillance data collection continuing beyond the close-out period until the end of the study. The date of visit, disease progression status, survival, and adverse events (AEs) will be reported at intervals of 6–12 months according to each center's policy. Quality of life (QoL) questionnaires will be administered at screening and at 1 and 2 years after randomization. The timeline for

https://doi.org/10.4048/jbc.2025.0157

	Study period								
	Enrollment & Allocation		Post-allocation						Close-out
Timepoint	−8 weeks	0 (Surgery)	6-months	1-year	1.5-year	2-year	3-year	4-year	5-year
Enrollment									
Eligibility screen	X								
Informed consent	X								
Allocation	X								
Interventions									
No-SLNB group: BCS		X							
SLNB group: BCS & SLNB		X							
Assessments									
Baseline demographic data	X								
Breast MRI	X		△	△	△	△	△	△	△
Breast ultrasound	X		△	△	△	△	△	△	△
Axillary ultrasound	X		△	△	△	△	△	△	△
Disease status			X	X	X	X	X	X	X
Adverse event status			X	X	X	X	X	X	X
EORTC QLQ-30	X			X		X			
EORTC QLQ-BR23	X			X		X			

Figure 2. Timeline for enrollment, interventions, and assessments.
X: mandatory, △: not mandatory.
SLNB = sentinel lymph node biopsy; BCS = breast-conserving surgery; MRI = magnetic resonance imaging; EORTC QLQ = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.

enrollment, interventions, and assessments is presented in **Figure 2** and formatted according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The corresponding SPIRIT checklist is shown in **Supplementary Table 2**.

Radiotherapy protocol

Whole-breast irradiation (WBI) is administered to all patients after surgery. In the SLNB group, the radiation field is determined at the discretion of a board-certified radiation oncologist at each participating center. In contrast, radiation planning was more strictly defined in the no-SLNB group. For patients with cN0 disease, either standard tangents or WBI with level I axillary coverage is required. For patients with cN1 disease, radiation field has to be selected from standard tangents, WBI with level I axillary coverage, high tangents, or regional nodal irradiation. Radiation dosing may follow either conventional fractionation (1.8–2.0 Gy per fraction, total dose 45.0–50.4 Gy over 23–28 fractions) or hypofractionated schedules (2.5–3.0 Gy per fraction, total dose 39.0–43.2 Gy over 13–16 fractions). In both groups, a tumor bed boost may be administered at the discretion of the treating physician, and target volumes may be adjusted within protocol-defined limits according to clinical judgment. Adherence to the radiotherapy protocol, particularly in the no-SLNB group, will be monitored through a centralized review of radiotherapy plans during the trial.

https://doi.org/10.4048/jbc.2025.0157

Study outcomes

The primary outcome is 5-year invasive disease-free survival (iDFS), defined as the time from the date of surgery to the first occurrence of one of the following events: invasive local, regional, or distant recurrence; invasive contralateral breast cancer; a second non-breast primary malignancy; or death from any cause. Events of carcinoma *in situ* (ipsilateral or contralateral breast or *in situ* malignancies of non-breast sites) are not included.

Secondary outcomes include: 1) 5-year overall survival (OS); 2) 5-year distant metastasis-free survival (DMFS); 3) 5-year ipsilateral axillary recurrence; 4) 5-year locoregional recurrence; and 5) patient-reported QoL, measured by the European Organization for Research and Treatment of Cancer Core QoL Questionnaire and breast cancer–specific module (EORTC QLQ-C30 and QLQ-BR23).

Safety monitoring

All AEs will be monitored and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. AEs are defined as any new medical issues that occur after randomization, excluding the natural progression of the underlying disease. Serious adverse events (SAEs) will be monitored as follows: any SAE must be reported to the principal investigator and the IRB within 24 hours of initial recognition by the investigator using the designated SAE report form. All SAEs will be followed until resolution or clinical stabilization. All other AEs will be documented and shared with the participating investigators on a quarterly basis. Any harm directly attributable to this clinical trial will be compensated in accordance with the clinical trial agreement and applicable insurance coverage.

Statistics

Sample size calculation

This study is a non-inferiority, randomized controlled trial designed to compare the outcomes between patients undergoing BCS with SLNB and those undergoing BCS without axillary surgery. The primary hypothesis is that omitting SLNB in selected patients after NST is not inferior to the standard SLNB approach in terms of iDFS. The assumed 5-year iDFS rate of 82% for the SLNB group is based on the published literature and institutional data on relapse-free survival (RFS), which was used as a surrogate because of the limited availability of iDFS-specific data in this setting. In a previous study of patients with stage II–III breast cancer and cytologically confirmed axillary lymph node metastasis, those who achieved ypN0 after NST had a 5-year RFS rate of 84% (95% confidence interval [CI], 80%–87%) [12]. Similarly, an analysis of our institutional database of patients with clinical T1–T3 and N0–N1 disease treated with NST and surgery between 2010 and 2018 showed a 5-year RFS of 84.1% and 75.6% in patients with ypN0 and residual nodal disease, respectively. Considering the expected inclusion of a substantial proportion of patients with cN0 in this trial and the use of iDFS as the primary endpoint, we conservatively assumed a 5-year iDFS rate of 82% in the control group.

The sample size was calculated using PASS 2022 software (non-inferiority tests for two survival curves using the log-rank test model). Assuming a one-sided significance level of 0.05, 80% power, a non-inferiority margin of 10%, and an expected 5-year iDFS rate of 82% in the SLNB group, 98 events were required to assess the primary outcome. Based on these assumptions, 215 patients were included in each group. Accounting for a conservative dropout rate of 7%, informed by the low loss to follow-up observed in our previous NAUTILUS trial, the target sample size was 464. Patients were recruited competitively across participating institutions.

https://doi.org/10.4048/jbc.2025.0157

Statistical analyses

All analyses will be conducted in the full analysis set (FAS), per-protocol (PP), and safety populations, as defined in the statistical analysis plan. The primary endpoint will be analyzed in both the FAS and PP populations, secondary endpoints in the FAS population, and safety outcomes in the safety population. If missing data occur, analyses will be performed using the available data without imputation.

For the primary endpoint (5-year iDFS), survival curves will be estimated using the Kaplan–Meier method, and the hazard ratio (HR) between the two groups will be calculated using Cox proportional hazards models. The adjusted HR will be estimated by stratifying clinical N stage and tumor subtype. In addition, covariates with a standardized mean difference exceeding $1.96 \times \sqrt{\frac{1}{Number\ of\ \text{SLNB group}} + \frac{1}{Number\ of\ no-\text{SLNB group}}}$ will be included for further adjustment. Non-inferiority will be concluded at a one-sided 5% significance level if the upper bound of the 90% CI for the adjusted HR is less than 1.655, which is the pre-specified non-inferiority margin.

Secondary endpoints (including OS, DMFS, ipsilateral axillary recurrence, and locoregional recurrence) will also be analyzed using the Kaplan–Meier method. QoL questionnaire scores will be compared between the two groups. All nominal variables will be assessed using the χ^2 or Fisher's exact test, and continuous variables will be analyzed using the Student's *t*-test or Mann–Whitney *U* test. For every statistical analysis, a *p*-value of < 0.05 will be considered statistically significant.

An interim analysis will be conducted after accrual completion to summarize recruitment, baseline characteristics, and early outcome trends. Early stopping for futility is not planned. The Medical Research Collaborating Center of Seoul National University Hospital will perform the statistical analyses.

Data collection, management, and monitoring

Investigators at each participating institution will collect clinical data, anonymize personal information, and enter the data into a secure electronic case report form. The principal investigator is responsible for study monitoring. To ensure data accuracy, safety, and completeness across all sites, an independent clinical research organization will conduct regular monitoring visits. In addition, a dedicated Data and Safety Monitoring Board will independently oversee data integrity and patient safety throughout the trial.

DISCUSSION

The NeoNAUTILUS trial is designed to determine whether axillary surgery can be safely omitted in patients predicted to have axillary nodal negativity after NST, particularly when BCS and whole-breast radiation are planned. Eligibility is based on predictors of axillary response proposed by Kim et al. [10] and predefined, stringent axillary ultrasound criteria derived from prior studies that correlated specific sonographic features, such as cortical thickness, nodal shape, hilum status, and vascularity, with pathologic nodal status [13,14]. These criteria were retrospectively validated and demonstrated a low rate of residual axillary disease after NST [9].

https://doi.org/10.4048/jbc.2025.0157

Concerns regarding the diagnostic accuracy of axillary ultrasound after NST have been raised, most notably in the recent AXillary Surgery After NeoAdjuvant Treatment (AXSANA) substudy [15], which reported limited sensitivity in predicting nodal status in broader cN1–3 populations. In contrast, NeoNAUTILUS focuses on a more favorable baseline cN0–cN1 cohort and applies more stringent, predefined sonographic criteria to mitigate the limitations observed in less-selected populations.

This study challenges the long-standing paradigm of routine axillary surgery in breast cancer treatment. Specifically, it examines whether axillary lymph node removal is necessary in patients with a very low risk of residual disease or in those with diseases unlikely affect recurrence or distant metastasis. The clinical relevance of this approach is heightened in the neoadjuvant setting, where NST is associated with increased rates of postoperative complications such as lymphedema [16]. Avoiding axillary surgery may provide both oncologic safety and functional benefits. Indeed, de-escalation of axillary surgery has already gained traction; for instance, in the Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer (I-SPY2) trial, the rate of axillary lymph node dissection in clinically node-positive patients declined from 70.7% in 2011 to 29.4% in 2021 [17], reflecting a global shift in surgical practice.

Several ongoing trials, including EUBREAST-01, ASICS, and ASLAN, are evaluating the omission of axillary surgery after NST. However, these studies are limited by their strict inclusion criteria, which typically required breast pCR, which significantly reducing the number of eligible patients. Moreover, the requirement for breast pCR creates logistical and clinical challenges when patients do not achieve pCR, often necessitating additional surgical procedures. While single-arm studies have demonstrated the feasibility of omitting axillary surgery in selected populations, randomized controlled trials are essential to establish definitive evidence of its efficacy and safety.

To address these limitations, NeoNAUTILUS is the first randomized trial to define eligibility based on the predicted axillary response rather than breast pCR. In our retrospective analysis, 95.2% of the patients who met the trial criteria achieved ypN0 despite a breast pCR rate of only 46.1%. Remarkably, even among patients without breast pCR, 91.5% had no residual nodal disease. These findings challenge the reliance on breast pCR as a surrogate marker of axillary status and provide strong support for the rationale underlying our study design.

A key concern in omitting axillary surgery is the potential loss of critical nodal information, which may influence adjuvant therapy decisions. In particular, undetected nodal disease in patients with breast pCR could lead to missed opportunities for adjuvant therapies such as capecitabine or T-DM1. However, our previous analysis showed that, among patients with breast pCR, the rate of residual nodal disease (ypN+) was only 0.55%. Even among patients with *in situ* disease (ypTis), the rate remained as low as 0.95%, reinforcing the safety of axillary omission in appropriately selected patients.

In conclusion, NeoNAUTILUS is the first randomized trial to prospectively evaluate the omission of axillary surgery after NST using rigorously validated selection criteria. Although the non-inferiority margin for 5-year iDFS was relatively wide at 10%, this threshold was selected to ensure feasible accrual in this highly selected population. This interpretation prioritizes clinical relevance and patient safety, and the results are expected to provide high-level evidence to guide future standards for the axillary management in breast cancer.

https://doi.org/10.4048/jbc.2025.0157

ACKNOWLEDGMENTS

The authors thank the Medical Research Collaborating Center at Seoul National University Hospital for their consultations.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

List of study sites

Supplementary Table 2

Standard Protocol Items: Recommendations for Interventional Trials 2013 checklist: recommended items to address in a clinical trial protocol and related documents

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