

Original Article



Long-term Outcomes of Early Breast Cancer Stratified by Axillary Ultrasound Assessment

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ABSTRACT

Purpose: De-escalation of axillary lymph node (ALN) surgery in early breast cancer is increasingly common. This study aimed to identify patients suitable for this approach by comparing long-term survival based on preoperative axillary ultrasound (AUS).

Methods: Patients undergoing surgery at Yonsei University Severance Hospital between January 2010 and December 2017 were categorized into “no suspicion” and “low suspicion” groups based on AUS findings.

Results: Median follow-up duration was 92 months. The 10-year recurrence-free survival (RFS) and overall survival rates for the no suspicion and low suspicion groups were 94.2% and 90.1% ($p < 0.001$) and 93.1% and 93.0% ($p = 0.177$), respectively. The 10-year locoregional RFS rates were 96.8% and 96.1% ($p = 0.060$). Among node-positive patients, 19.9% in the no suspicion group had three or more metastatic ALNs compared with 23.0% in the low suspicion group ($p = 0.012$). Recurrence was associated with T stage, N stage, histologic grade, Ki-67, and subtype, whereas mortality was linked to age, T stage, N stage, histologic grade, and subtype.

Conclusion: The low suspicion and fine-needle aspiration biopsy-negative group had poorer prognostic biomarkers, leading to differences in recurrence but not in overall survival. The preoperative ALN status did not affect survival rates. Even in patients with cT2 and low suspicion of ALN, the rate of three or more metastatic ALNs was low, suggesting that further axillary surgery may not be necessary if two or fewer metastatic lymph nodes are found in the sentinel lymph node.

Keywords: Breast Neoplasms; Lymphatic Metastasis; Neoplasm Staging; Survival; Ultrasonography

INTRODUCTION

Surgery is the primary treatment for early-stage breast cancer [1]. Standard breast cancer surgery involves radical local excision of the malignant breast tumor and axillary lymph node (ALN) surgery [2]. Metastatic lymph nodes (LNs) are removed through axillary surgery, and staging is performed to plan adjuvant systemic treatments and predict prognosis. Various clinical studies have confirmed that further axillary lymph node dissection (ALND) is

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Conflict of Interest

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Data Availability

In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request.

Author Contributions

Conceptualization: Kim SI, Park S; Data curation: Lee SJ, Ahn JH, Kim JY, Park HS, Kim SI; Formal analysis: Yoon KH; Software: Yoon KH; Supervision: Park S; Writing - original draft: Yoon KH; Writing - review & editing: Yoon KH.

unnecessary in cases of clinically node-negative breast cancer, even if metastasis is confirmed [3-5]. Furthermore, sentinel lymph node biopsy (SLNB) may be safely omitted without compromising oncological safety in patients with early breast cancer with no suspicious findings on preoperative axillary ultrasound (AUS) [6]. For clinical N0 early breast cancer, various randomized controlled trials (RCTs) have established guidelines for axillary surgery. Therefore, it is necessary to evaluate whether ALN surgery can be modified based on the severity of the abnormalities detected by AUS in clinically node-positive T2 or smaller breast cancer patients.

The most important assessment tool for classifying patients as clinically node negative before treatment is AUS [7]. Ultrasonography is a fundamental assessment modality for the preoperative evaluation of breast cancer. AUS is cost-effective, non-invasive, and can be performed concurrently with the evaluation of breast lesions [8]. ALN assessment using AUS typically involves the evaluation of several factors that determine the presence of metastasis, including LN size, shape, margins, cortical thickness, hilum, echogenicity, and vascularity [9]. In cases where suspicious findings are observed on preoperative AUS, fine-needle aspiration biopsy (FNAB) enables pathological confirmation of LN metastasis, thereby enhancing assessment accuracy [10]. This workup of clinical axillary status allows for either upfront surgery, including SLNB or ALND, or neoadjuvant systemic therapy and other procedures [2]. According to the National Comprehensive Cancer Network (NCCN) guidelines, the panel recommends performing SLNB in cases with two or fewer positive LNs on AUS or FNAB. If the sentinel lymph node (SLN) is negative, no further surgeries are required. However, there is a lack of research and RCTs providing evidence on axillary staging and surgery in patients with clinically node-positive breast cancer.

By comprehensively evaluating the preoperative axillary status, it is possible to distinguish between cN0 and cN+ and further classify the risk within suspicious nodes [11]. No suspicious LN, low suspicious LN, highly suspicious LN on AUS, and metastatic LN on FNAB represent different clinical nodal statuses [12]. However, in clinical practice, these AUS findings are often interchangeable. These scenarios can be considered equivalent when making decisions regarding axillary surgery. It is essential to review the long-term follow-up outcomes of patients with clinically low suspicious ALN metastasis. This study aimed to categorize patients with early breast cancer scheduled for upfront surgery based on AUS results and to evaluate the oncologic outcomes associated with these classifications.

METHODS

Patient selection and clinicopathologic characteristics

Patients with primary invasive breast cancer who underwent upfront surgery between January 2010 and December 2017 were retrospectively selected from the medical database of Yonsei University Severance Hospital (Seoul, Korea). Patients who underwent preoperative AUS were included. The exclusion criteria were *de novo* stage IV disease, pathologic Tis, preoperative clinical T3 or higher, neoadjuvant chemotherapy, non-epithelial origin cancer, highly suspicious LN on AUS or metastatic LN on FNAB, occult breast cancer, and the absence of axillary surgery. A total of 4,248 patients were included in this retrospective study to evaluate the clinical implications of the preoperative ALN status. Based on the AUS and FNAB results, the patients were categorized into two groups: those with either no suspicious findings on AUS or low suspicious findings on AUS, which included negative

or nondiagnostic FNAB results. The medical database cataloged patient characteristics, including age at diagnosis, as well as postoperative pathological results such as histological type; nuclear grade; histological grade (HG); tumor size; number of LN metastases; estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression; and Ki-67 index. HG was assessed using the modified Bloom-Richardson grading system [13]. Tumors were classified as positive for ER and PR if they demonstrated $\geq 1\%$ of nuclear-stained cells [14]. Data on treatment-related factors, including antihormone therapy, HER2-targeted treatment, adjuvant chemotherapy, radiotherapy, and breast surgery, were also included. The data also encompassed oncological outcomes related to survival, recurrence, and mortality.

This project was reviewed and approved by the Institutional Review Board (IRB) of Yonsei University Severance Hospital (IRB No. 4-2023-0746). The need for informed consent was waived because of the retrospective nature of the study.

Outcome and definition

Data were retrospectively analyzed to compare overall survival (OS) and recurrence-free survival (RFS) in the study population. OS was defined as the period between surgery and death due to any cause [15]. RFS was defined as the period between surgery and the first local, regional, or distant tumor recurrence. Second primary cancers, contralateral breast cancer, and deaths with no evidence of disease were treated as censoring events. Local recurrence was defined as the reappearance of cancer at the original tumor site after treatment, including the skin, pectoral muscles, deeper chest wall, surgical site, or a different quadrant of the breast. Regional recurrence involved cancer re-emergence in the ipsilateral ALN, supraclavicular LN, or internal mammary LN. RFS was included in this analysis, as it may serve as a more relevant outcome than disease-free survival for assessing progression in clinically node-negative or low suspicious early breast cancer patients. ALN assessment by AUS was classified as either low suspicious or highly suspicious, according to the criteria of the ongoing NAUTILUS clinical trial [16]. Low suspicious ALN was defined as an increase in cortical thickness > 3 mm, whereas highly suspicious ALN was characterized by the complete disappearance of the LN hilum fat, tumor invasion of the entire LN hilum, extracapsular extension of LN involvement, and microcalcifications within the LN. The primary outcomes were to identify factors associated with ALN metastasis in clinically node-negative or low suspicious early breast cancer patients. The secondary outcomes involved assessing survival outcomes according to the clinical axillary nodal status.

Data and statistical analysis

Continuous clinicopathological variables were converted into binary or multinomial variables for analysis based on medical evidence or distribution. For binary or multinomial variables, the χ^2 test or Fisher exact test was used for comparison. The Kaplan-Meier method was used to estimate survival curves, and differences were assessed using the log-rank test. The hazard ratios and 95% confidence intervals were estimated for each variable using the Cox univariate model. Multivariate Cox proportional hazard regression models were used to determine the factors that affected the survival rates between the groups. A multivariate model was developed by considering the interaction between significant variables. SPSS software (version 29.0; IBM Inc., Armonk, USA) was used for all statistical analyses.

RESULTS

Characteristics of patients

In the cohort of early breast cancer patients who underwent AUS and upfront surgery, 3,790 (89.2%) were categorized as having no suspicious findings on AUS and 458 (10.8%) as having low suspicious findings on AUS (**Figure 1**). The baseline characteristics and treatment details of the 4,248 total patients, according to the AUS results are summarized in **Table 1**. The low suspicious findings on AUS group, which had a higher proportion of T2 tumors and node metastasis, demonstrated a greater tumor burden. HG and Ki-67, factors traditionally associated with a poor prognosis, were also higher in the low suspicious group. Compared with the cN0 group, the low suspicious findings on AUS group showed a higher proportion of hormone receptor negative (HR-)/HER2 positive (HER2+) and triple-negative breast cancers ($p < 0.001$). The rates of ALND and adjuvant chemotherapy were also higher in the low suspicious on AUS group (**Supplementary Table 1**).

ALN metastasis

Among all patients, 735 (17.3%) had LN metastasis. The proportions of node metastasis in the two groups were 622/3,790 (16.4%) versus 113/458 (24.7%) ($p < 0.001$). Among node-positive patients, the proportion with three or more metastatic LNs in SLN or one or more metastatic LN in non-SLN was 180/622 (28.9%) and 33/113 (29.3%), respectively ($p = 0.876$). As the number of positive SLNs increased in each group, the total number of metastatic ALNs increased. However, the proportion of three or more total metastatic ALNs was not statistically different between the two groups (**Table 2**). In early breast cancer patients who underwent upfront surgery, univariate analysis revealed that younger age, larger malignant tumors, low suspicion on AUS, and subtype were associated with LN metastasis (**Table 3**). Multivariate analysis demonstrated that T stage, AUS status, and subtype were independently associated with LN metastasis. Both groups had a low overall rate of metastasis, and the rate of three or more ALN metastases was also low.

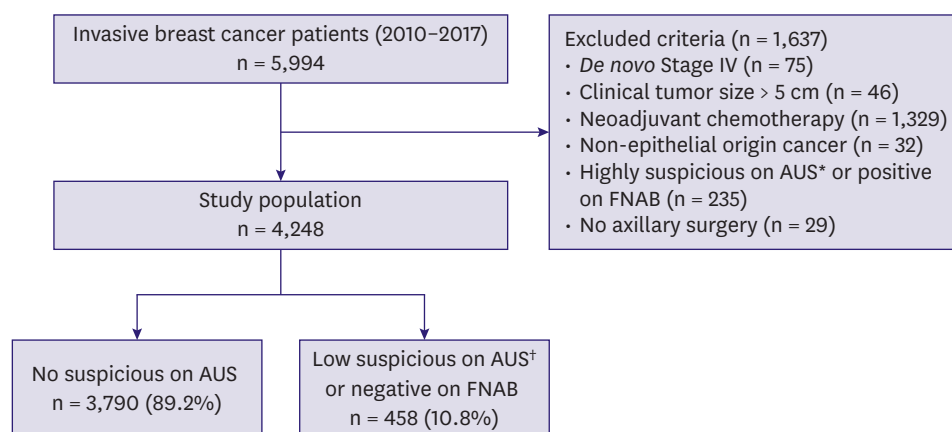


Figure 1. Scope of study population.

LN = lymph node; AUS = axillary ultrasound; FNAB = fine-needle aspiration biopsy.

*Complete disappearance of LN hilum fat, tumor invasion of the entire LN hilum, extracapsular extension of LN involvement, or microcalcifications within the LN.

[†]Increase in cortical thickness > 3 mm.

Table 1. Clinicopathological characteristics by results of preoperative axillary ultrasound

Characteristics	No suspicious on AUS (n = 3,790)	Low suspicious on AUS (n = 458)	p-value
Age			< 0.001
Age ≤ 50	1,744 (46.0)	252 (55.0)	
Age > 50	2,046 (54.0)	206 (45.0)	
T stage			< 0.001
T1	3,045 (80.3)	291 (63.5)	
T2	745 (19.7)	167 (36.5)	
N stage			< 0.001
N0	3,168 (83.6)	345 (75.3)	
N1mi	170 (4.5)	27 (5.9)	
N1	378 (10.0)	68 (14.8)	
N2	62 (1.6)	15 (3.3)	
N3	12 (0.3)	3 (0.7)	
Stage			< 0.001
I	2,753 (72.7)	243 (53.1)	
II	960 (25.3)	197 (43.0)	
III	77 (2.0)	18 (3.9)	
Histologic grade			< 0.001
Grade 1	1,079 (28.5)	71 (15.5)	
Grade 2	1,985 (52.4)	216 (47.2)	
Grade 3	726 (19.2)	171 (37.3)	
Ki-67			< 0.001
Ki-67 ≤ 20	2,699 (71.2)	241 (52.6)	
Ki-67 > 20	1,019 (26.9)	207 (45.2)	
Missing	71 (1.9)	10 (2.2)	
Subtype			< 0.001
HR+/HER2-	2,758 (72.8)	242 (52.8)	
HR+/HER2+	340 (9.0)	47 (10.3)	
HR-/HER2+	252 (6.6)	71 (15.5)	
Triple-negative	440 (11.6)	98 (21.4)	
Breast operation			< 0.001
Breast conserving surgery	2,505 (66.1)	223 (48.7)	
Mastectomy	1,285 (33.9)	235 (51.3)	
Axillary operation			< 0.001
SLNB	3,245 (85.6)	351 (76.6)	
ALND	545 (14.4)	107 (23.4)	
Adjuvant chemotherapy	1,862 (49.1)	342 (74.7)	< 0.001
Radiation treatment	2,649 (69.9)	267 (58.3)	< 0.001
All deaths	166 (4.4)	28 (6.1)	0.063
All recurrence	189 (5.0)	40 (8.7)	< 0.001

Values are presented as number of patients (%).

AUS = axillary ultrasound; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR- = hormone receptor negative; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection.

Survival outcome according to clinical nodal status

The median follow-up duration was 92 months. RFS was statistically significantly different between the two groups (10-year RFS: no suspicious findings on AUS vs. low suspicious findings on AUS = 94.2% vs. 90.1%, $p < 0.001$) (**Figure 2**). Factors associated with recurrence were analyzed in the entire patient cohort (**Table 4**). In the univariate analysis, the factors associated with recurrence included T stage, N stage, HG, Ki-67, AUS status, and subtype. Multivariate analysis identified T stage, N stage, HG, Ki-67, and tumor subtype as factors related to recurrence.

On the other hand, OS showed no statistically significant difference between the no suspicious on AUS group and the low suspicious on AUS group (10-year OS: 93.1% vs. 93.0%, $p = 0.177$). In the univariate analysis, age, T stage, N stage, HG, Ki-67, and subtype were found

Table 2. Lymph node features

Characteristics	No suspicious on AUS (n = 3,790)	Low suspicious on AUS (n = 458)	p-value
ALN status			
Retrieved SLN	4 (3–5)	5 (3–7)	< 0.001
Retrieved ALN in ALND patients	14 (11–19)	15 (12–20)	< 0.001
Pathological axillary nodal burden based on the number of metastatic SLN			
One metastatic SLN	12.3% (468/3,790)*	18.3% (84/458)*	0.198
No metastatic ALN [†]	366 (78.2) [‡]	67 (79.8) [‡]	
One metastatic ALN	57 (12.2) [‡]	9 (10.7) [‡]	
Two or more metastatic ALN	45 (9.6) [‡]	8 (9.5) [‡]	
Two metastatic SLN	2.9% (111/3,790)*	4.1% (19/458)*	0.998
No metastatic ALN [†]	76 (68.5) [‡]	13 (68.4) [‡]	
One metastatic ALN	18 (16.2) [‡]	3 (15.8) [‡]	
Two or more metastatic ALN	17 (15.3) [‡]	3 (15.8) [‡]	
Three or more metastatic SLN	1.1% (43/3,790)*	2.2% (10/458)*	0.098
No metastatic ALN [†]	9 (20.9) [‡]	3 (30.0) [‡]	
One metastatic ALN	14 (32.6) [‡]	1 (10.0) [‡]	
Two or more metastatic ALN	20 (46.5) [‡]	6 (60.0) [‡]	

Values are presented as median (interquartile range) not otherwise specified.

AUS = axillary ultrasound; ALN = axillary lymph node; SLN = sentinel lymph node; ALND = axillary lymph node dissection.

*The data is presented as percentages, where within the parentheses, the denominator represents the total number of patients for each selected AUS status, and the numerator denotes the number of patients with the corresponding total SLN metastasis count.

[†]Including patients for whom ALND was omitted.

[‡]The data is presented as patient numbers, where within the parentheses, the denominator represents the total number of patients for each selected SLN metastasis count, and the numerator denotes the number of patients with the corresponding total number of metastatic ALNs in further dissection.

Table 3. Clinicopathological factor associated with axillary lymph node metastasis

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
Age ≤ 50	Reference		Reference	
Age > 50	0.844 (0.721–0.991)	< 0.037	0.912 (0.774–1.073)	0.267
T stage				
T1	Reference		Reference	
T2	2.383 (2.003–2.835)	< 0.001	2.391 (1.994–2.868)	< 0.001
Histologic grade				
Grade1	Reference		Reference	
Grade2	1.252 (1.034–1.517)	0.021	1.241 (1.018–1.513)	0.033
Grade 3	0.997 (0.784–1.268)	0.978	1.095 (0.823–1.457)	0.534
Ki-67				
Ki-67 ≤ 20	Reference			
Ki-67 > 20	0.952 (0.798–1.136)	0.586		
AUS				
No suspicious on AUS	Reference		Reference	
Low suspicious on AUS	1.668 (1.327–2.098)	< 0.001	1.627 (1.277–2.072)	< 0.001
Subtype				
HR+/HER2–	Reference		Reference	
HR+/HER2+	0.875 (0.661–1.157)	0.349	0.794 (0.592–1.065)	0.123
HR–/HER2+	0.724 (0.525–1.000)	0.050	0.627 (0.444–0.886)	0.008
Triple-negative	0.445 (0.329–0.603)	< 0.001	0.383 (0.273–0.538)	< 0.001

OR = odds ratio; CI = confidence interval; AUS = axillary ultrasound; HR+ = hormone receptor positive; HER2– = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR– = hormone receptor negative.

to be associated with mortality. Multivariate analysis identified age, T stage, N stage, HG, and subtype as determinants of death (**Table 5**).

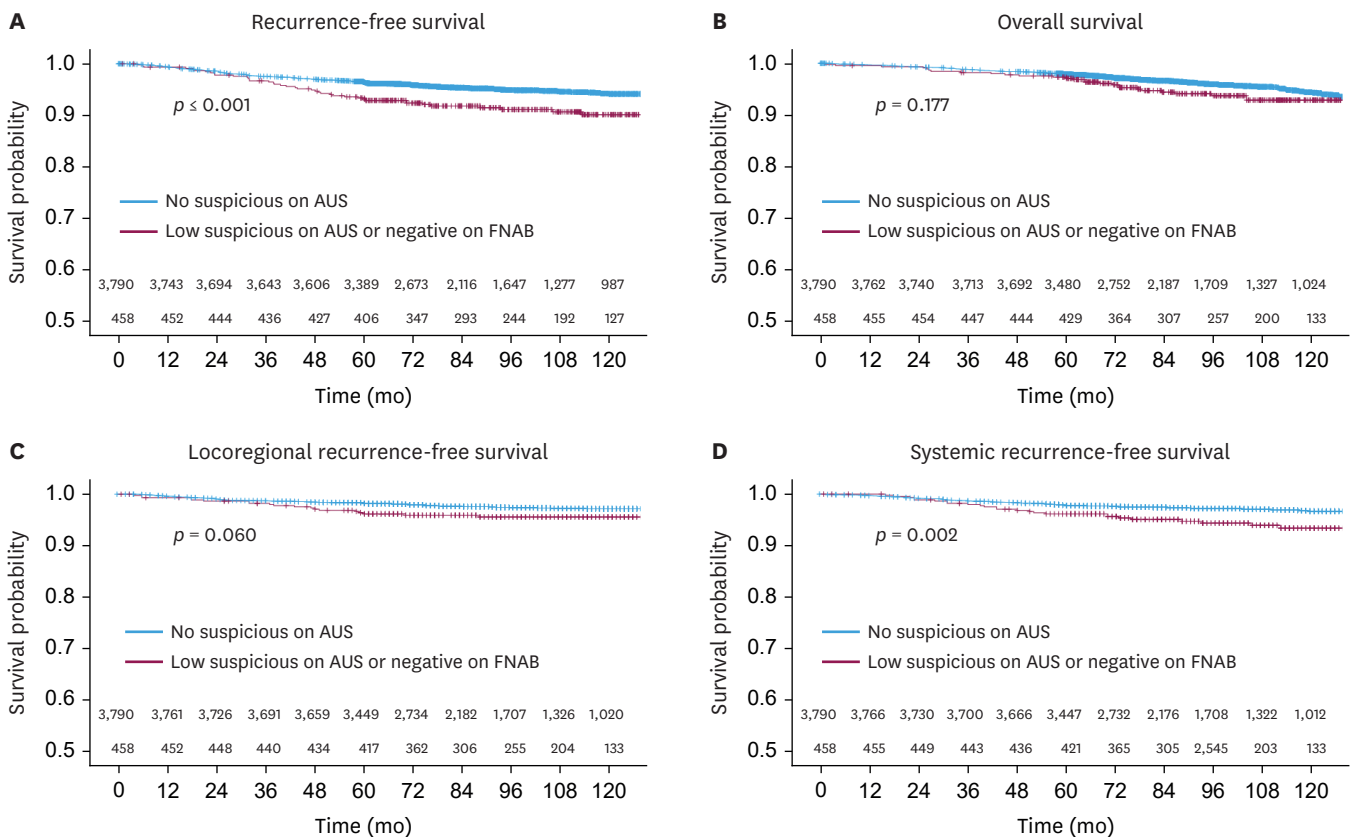


Figure 2. Survival outcome according to axillary ultrasound and fine-needle aspiration biopsy results.

(A) Relapse-free survival, (B) overall survival, (C) locoregional relapse-free survival, and (D) systemic relapse-free survival.

AUS = axillary ultrasound; FNAB = fine-needle aspiration biopsy.

RFS was further analyzed by categorizing it into locoregional recurrence-free survival (LRRFS) and systemic recurrence-free survival (SRFS). For systemic recurrence, the statistical difference observed in RFS was maintained (10-year SRFS: 96.2% vs. 94.3%, $p = 0.002$), whereas for locoregional recurrence, there was no significant difference between the cN0 and cN+ groups (10-year LRRFS: 96.8% vs. 96.1%, $p = 0.060$). The low suspicion on AUS group showed worse outcomes in terms of recurrence, but there was no difference in locoregional metastasis and mortality rates. Furthermore, the AUS status was not related to either recurrence or mortality rates in the entire cohort.

DISCUSSION

The trend in treating early breast cancer has been toward de-escalation, which reduces the intensity of therapy while maintaining non-inferior survival outcomes [17]. In the era of Halsted, surgical outcomes varied depending on the extent and nuances of the surgery, leading to the widespread practice of extensive ALND [18]. The introduction of SLNB in breast cancer significantly reduced the surgical extent of early breast cancer [19]. Moreover, following the Z0011 trial, further dissection was no longer performed in selected cases even when LN metastasis was confirmed [4]. Additionally, clinical trials that omitted SLNB in early breast cancer patients with no suspicious findings on AUS confirmed no difference in survival rates [6]. With the accumulation of expertise and research on preoperative AUS, the prediction of

Table 4. Univariate and multivariate analyses of relapse-free survival in the entire patient cohort

Variables	Relapse-free survival			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age				
Age ≤ 50	Reference		-	
Age > 50	0.793 (0.612–1.029)	0.080	-	
T stage				
T1	Reference		Reference	
T2	2.527 (1.940–3.291)	< 0.001	1.963 (1.480–2.604)	< 0.001
N stage				
N0	Reference		Reference	
N1	1.675 (1.217–2.306)	0.002	1.619 (1.161–2.257)	0.005
N2, N3	4.238 (2.571–6.984)	< 0.001	3.173 (1.844–5.459)	< 0.001
Histologic grade				
Grade 1	Reference		Reference	
Grade 2	2.324 (1.551–3.480)	< 0.001	1.723 (1.012–2.841)	0.004
Grade 3	3.447 (2.246–5.292)	< 0.001	1.860 (1.217–2.934)	0.045
Ki-67				
Ki-67 ≤ 20	Reference		reference	
Ki-67 > 20	2.071 (1.587–2.701)	< 0.001	1.414 (1.011–1.978)	0.043
AUS				
No suspicious on AUS	Reference		Reference	
Low suspicious on AUS	1.714 (1.218–2.411)	0.002	1.148 (0.799–1.648)	0.445
Subtype				
HR+/HER2–	Reference		Reference	
HR+/HER2+	1.329 (0.853–2.068)	0.208	1.034 (0.648–1.648)	0.891
HR–/HER2+	1.414 (0.884–2.263)	0.075	1.104 (0.670–1.821)	0.697
Triple-negative	2.268 (1.650–3.118)	< 0.001	1.711 (1.147–2.551)	0.008

CI = confidence interval; AUS = axillary ultrasound; HR+ = hormone receptor positive; HER2– = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR– = hormone receptor negative.

ALN status before treatment has improved [20]. By comparing the long-term outcomes of patients with low suspicious ALN findings on preoperative AUS with those without, we aimed to identify patient groups for whom de-escalation of axillary surgery was feasible.

According to the data from this study, the low suspicious ALN group had a higher proportion of factors associated with poor prognosis. These differences resulted in statistically significant differences in the recurrence rates between the two groups during long-term follow-up. However, there were no significant differences in locoregional recurrence or OS. Mortality was associated with older age, anatomical stage, and HG, whereas recurrence was associated with anatomical stage, HG, Ki-67, and subtype in multivariate analysis. As is widely known, tumor burden, HG, Ki-67, and subtype are powerful factors in predicting breast cancer prognosis [21]. The preoperative AUS status was not statistically significant in multivariate analysis for long-term recurrence and OS. Although the pathological nodal burden varied depending on AUS status, there was no difference in OS outcomes when appropriate local and systemic treatments were implemented). Both groups showed good results in terms of the 10-year OS. The low suspicious group had a higher recurrence rate than the no suspicious group, mainly due to systemic recurrence, whereas locoregional recurrence showed no statistical difference. These findings suggest that appropriate treatment following recurrence can still result in good survival outcomes.

For clinical N0 early breast cancer, axillary surgery strategies should be based on the results of the NSABP B-32, Z0011, SINODAR-ONE, and SOUND trials [3–6,19]. These RCTs

Table 5. Univariate and multivariate analyses of overall survival in the entire patient cohort

Variables	Overall survival			
	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age				
Age ≤ 50	Reference		Reference	
Age > 50	1.978 (1.463–2.675)	< 0.001	1.989 (1.458–2.713)	< 0.001
T stage				
T1	Reference		Reference	
T2	2.076 (1.550–2.780)	< 0.001	1.727 (1.261–2.366)	< 0.001
N stage				
N0	Reference		Reference	
N1	1.527 (1.071–2.177)	0.019	1.493 (1.032–2.158)	0.033
N2, N3	3.612 (2.047–6.374)	< 0.001	2.802 (1.498–5.240)	0.001
Histologic grade				
Grade 1	Reference		Reference	
Grade 2	1.663 (1.122–2.463)	0.011	1.604 (1.059–2.429)	0.026
Grade 3	2.350 (1.537–3.594)	< 0.001	2.051 (1.187–3.542)	0.010
Ki-67				
Ki-67 ≤ 20	Reference		Reference	
Ki-67 > 20	1.465 (1.083–1.983)	0.013	1.063 (0.720–1.571)	0.758
AUS				
No suspicious on AUS	Reference		-	
Low suspicious on AUS	1.317 (0.882–1.965)	0.178	-	
Subtype				
HR+/HER2-	Reference		Reference	
HR+/HER2+	0.754 (0.426–1.333)	0.332	0.612 (0.340–1.102)	0.102
HR-/HER2+	0.865 (0.479–1.562)	0.631	0.656 (0.351–1.223)	0.185
Triple-negative	1.646 (1.151–2.354)	0.006	1.152 (0.733–1.831)	0.539

CI = confidence interval; AUS = axillary ultrasound; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HER2+ = human epidermal growth factor receptor 2 positive; HR- = hormone receptor negative.

demonstrated that ALND was not necessary if the SLNB was negative [3,19]. Moreover, in selected patients, even those with SLN metastasis, additional ALN surgery may not be required [4,5]. In cases in which the clinical T is less than 2 cm, breast surgery alone without SLNB may be sufficient [6]. In the NSABP B-32 trial, the overall accuracy of SLNB in the control group was 97.1%, with a false-negative rate of 9.8%. During the 8-year follow-up, the regional node recurrence rate in the control group was only 0.4% [3]. Additionally, in the Z0011 trial, 23.7% of the ALND group had additional positive LNs other than SLN [4]. In the SINODAR-ONE trial, this figure was even higher, at 44.0%, but there was no difference in survival outcomes [5]. Even in cN0 and cT1 or smaller breast cancer patients scheduled for breast-conserving surgery and radiation therapy, 13.7% who underwent SLNB were found to have axillary metastasis, yet their survival rates were comparable to those who did not undergo SLNB [6]. Our data included patients with clinical T2 or smaller breast cancer and clinically low suspicious ALN, showing a higher rate of LN metastasis than the SOUND trials. However, compared to the SINODAR-ONE and Z0011 trials, the proportion of patients with three or more metastatic LNs in SLN or positive LNs in non-SLN was lower. This suggests that even in patients with cT2 and low suspicious ALN, if there were two or fewer metastatic LNs in the SLN, further axillary surgery might not have been necessary. Additionally, if there were a few suspicious findings on AUS but FNAB was negative, SLNB omission could have been considered for some patients.

Extensive studies have been conducted to avoid further axillary dissection in clinically node-positive breast cancer patients. One study reported that among 141 women with suspicious

axillary imaging and positive FNAB, 47% had only one or two positive LNs on final pathology [22]. In another study, approximately 44% of FNAB-positive patients on preoperative imaging had one or two LN metastases, closely associated with the number of suspicious LNs observed on imaging [23]. A study using the National Cancer Database compared the survival outcomes among clinically node-positive patients who underwent SLNB and regional nodal irradiation (RNI), ALND and RNI, or ALND alone. Among the clinically node-positive and T1–2 breast cancer patients, those who underwent SLNB and RNI did not have inferior survival compared with those who underwent ALND [24]. Additionally, data from the National Cancer Database from 2018 to 2020 showed that approximately one-third of patients with ≥ 3 positive SLNs did not undergo ALND. This study found that older age, lower-grade tumors, breast conserving surgery, more SLNs examined, and fewer positive SLNs were significantly associated with omission of ALND [25]. These retrospective studies suggest that for selected patients with cN+ T2 or smaller breast cancer, further dissection is unnecessary, even if SLNB is positive. Our research also indicates that the omission of ALND in cN+ patients does not affect long-term survival.

For long-term survival analysis of early-stage breast cancer, it is necessary to consider both clinicopathological factors and treatment [26]. Based on patient factors, anatomical stage, and breast cancer subtype, physicians determine appropriate locoregional and systemic treatments. Our data analysis revealed that locoregional treatments such as surgery and radiation therapy were appropriately administered in most cases, regardless of age or subtype (**Supplementary Table 1**). Endocrine and HER2-targeted treatments were also appropriately administered based on hormone receptor and HER2 status, respectively. However, systemic chemotherapy approaches were tailored based on factors such as patient age, cancer subtype, and stage. Younger breast cancer patients were more frequently treated with chemotherapy for all subtypes. However, the HR positive (HR+)/HER2 negative (HER2–) subtype, despite a higher rate of node metastasis, had the lowest rate of adjuvant chemotherapy. Despite nodal metastasis, some patients with this subtype may achieve a favorable prognosis with endocrine therapy alone, without chemotherapy. However, this should not be interpreted as disregarding ALN metastasis; nodal status remains a strong prognostic factor, as confirmed by our data. By analyzing treatment and survival based on the preoperative ALN status in early breast cancer, appropriate treatment can lead to a favorable prognosis. Guidelines for axillary surgery in cN0 breast cancer patients are evolving in line with current surgical trends. Therefore, it is essential to consider the therapeutic and prognostic effects of ALN surgery in cN+ breast cancer patients.

Compared to other subtypes, the prognosis of HR+/HER2– subtypes is relatively favorable, and good outcomes can be expected even without chemotherapy in some cases [27]. However, according to the recently published RxPONDER and updated MINDACT trials, adding chemotherapy to endocrine therapy in premenopausal women or those aged < 50 years with ALN metastasis improves survival rates [28,29]. In these patients, nodal status serves as a predictive marker for adjuvant chemotherapy. Therefore, based on the postoperative pathology in HR+/HER2– breast cancer, it is necessary to assess the risk and consider additional systemic treatments, such as endocrine therapy, ovarian function suppression, adjuvant chemotherapy, or targeted therapies, such as cyclin-dependent kinase 4/6 inhibitors, if needed. De-escalation of axillary surgery in young patients with HR+/HER2– breast cancer should be approached with caution.

Our study has several limitations. First, as this was a retrospective study, selection bias may have occurred. The study design limited the ability to determine the efficacy of specific treatment methods. Although our data and landmark clinical trials suggest that axillary surgery omission is feasible in selected patients, confirming the outcomes of this approach is challenging. Additionally, owing to the study design and IRB approval, it was not possible to determine the number of suspicious LNs. The presence of fewer than two or two or more suspicious LNs would have affected the pathological nodal stage; however, analyzing this aspect was challenging. In this study, we analyzed the number of metastatic SLNs and total number of metastatic ALNs after further dissection. Alternatively, the ratio of metastatic to harvested SLN counts could be a useful indicator for predicting non-SLN metastasis, especially in patients with two or fewer SLNs; however, this was difficult to evaluate in our dataset [30]. Furthermore, because of the retrospective nature of this study, it was difficult to ascertain the effects of specific chemotherapy and endocrine therapy modalities. The high incidence of breast cancer in young premenopausal women in Korea has led to excessive administration of systemic chemotherapy. Most clinical trials that inform treatment guidelines involve an older age distribution than that in our dataset. Young patients were sometimes treated according to protocols designed for older patients, potentially leading to less aggressive treatments than younger patients require. To analyze long-term survival data, including those of patients treated in the past, systemic therapy was sometimes administered more aggressively than current guidelines would suggest. However, our study is meaningful because, compared with meticulously structured clinical trials, it encompasses a wide variety of patient groups across ages, subtypes, and anatomical stages of early breast cancer. Our study focused on the long-term follow-up of cN0 and low suspicious ALN breast cancer patients who underwent upfront surgery, and the results indicated that adherence to treatment guidelines leads to an excellent prognosis.

Compared to the no suspicious ALN group, the low suspicious ALN and FNAB-negative group tended to have more biomarkers related to poor prognosis. As a result, differences in recurrence rates were observed, but there were no significant differences in locoregional recurrence or OS during the long-term follow-up. Additionally, preoperative ALN status did not affect the survival rates of patients with early breast cancer. Compared with cN0 patients in major clinical trials, the low suspicious ALN group did not have a high rate of three or more SLN metastases or non-SLN metastases. Even in cases with a low suspicious ALN, omission of ALND should be considered. However, such decisions should be made with caution in young patients with luminal HER2- breast cancer.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Clinicopathological characteristics and treatment according to subtype and age of clinically node-negative breast cancer patients

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