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Survival Outcomes Based on Axillary Surgery in Ductal Carcinoma *In Situ*: A Nationwide Study From the Korean Breast Cancer Society

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ABSTRACT

Purpose: In total mastectomy (TM), sentinel lymph node biopsy (SLNB) is recommended but can be omitted for breast-conserving surgery (BCS) in patients with ductal carcinoma *in situ* (DCIS). However, concerns regarding SLNB-related complications and their impact on quality of life exist. Consequently, further research is required to evaluate the role of axillary surgeries, including SLNB, in the treatment of TM. We aimed to explore the clinicopathological factors and outcomes associated with axillary surgery in patients with a final diagnosis of pure DCIS who underwent BCS or TM.
Methods: We retrospectively analyzed large-scale data from the Korean Breast Cancer Society registration database, highlighting on patients diagnosed with pure DCIS who underwent surgery and were categorized into two groups: BCS and TM. Patients were further categorized into surgery and non-surgery groups according to their axillary surgery status. The analysis compared clinicopathological factors and outcomes according to axillary surgery status between the BCS and TM groups.
Results: Among 18,196 patients who underwent surgery for DCIS between 1981 and 2022, 11,872 underwent BCS and 6,324 underwent TM. Both groups leaned towards axillary surgery more frequently for large tumors. In the BCS group, clinical lymph node status was associated with axillary surgery (odds ratio, 11.101; $p = 0.003$). However, in the TM group, no significant differences in these factors were observed. Survival rates did not vary between groups according to axillary surgery performance.
Conclusion: The decision to perform axillary surgery in patients with a final diagnosis of pure DCIS does not affect the prognosis, regardless of the breast surgical method. Furthermore, regardless of the breast surgical method, axillary surgery, including SLNB, should be considered for high-risk patients, such as those with large tumors. This may reduce unnecessary axillary surgery and enhance the patients' quality of life.

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Conflict of Interest
The authors declare that they have no competing interests.

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 BK, Lee J[1], Sun WY; Data curation: Kim BK, Lee J[1]; Formal analysis: Kim BK; Investigation: Kim BK, Lee J[1]; Methodology: Kim BK, Sun WY; Resources: Kim BK, Woo J, Lee J[2], Kang E, Baek SY, Lee S, Lee HJ, Lee J[1], Sun WY; Supervision: Sun WY; Writing - original draft: Kim BK; Writing - review & editing: Sun WY.

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INTRODUCTION

In South Korea, the incidence of ductal carcinoma *in situ* (DCIS) has been steadily increasing due to early screening [1]. Furthermore, the rate of mastectomy for DCIS has increased, partly because of the expansion of insurance coverage for breast reconstruction after total mastectomy (TM) for breast cancer [2]. In cases where TM is performed for DCIS, clinical reasons include considerations such as a large tumor size or the presence of extensive microcalcifications, including non-clinical reasons such as cosmetic concerns and patient preferences, even when the tumor is localized enough to be adequately treated with breast-conserving surgery (BCS) [3].

Sentinel lymph node biopsy (SLNB) is performed in cases where breast surgery is conducted at anatomical locations where the lymphatic fluid drainage into the axilla may be compromised due to surgery [4-6]. Accordingly, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend omitting SLNB for BCS but recommending SLNB for TM in the context of DCIS [7,8].

DCIS does not breach the basement membrane and, therefore, does not involve invasion or metastasis. In reality, the rate of axillary lymph node metastasis in patients with pure DCIS is < 2%. Furthermore, 13.3%–37.9% of cases diagnosed with DCIS after surgical resection and upon final pathological examination are upgraded to microinvasive carcinoma [9-15]. This indicates the possibility of lymph node involvement, which may be overlooked if an SLNB is not performed. SLNB helps confirm axillary lymph node metastasis in invasive breast cancer, potentially allowing the omission of additional axillary lymph node dissection and preventing postoperative complications. However, SLNB itself can lead to complications such as lymphedema, restricted range of motion, sensory deficits, wound infections, hematomas, seromas, and other issues [16-18]. SLNB alone can lead to a decline in Global Health Status Quality of Life score [19].

Currently, there is paucity of large-scale studies in South Korea exploring the clinical differences based on axillary surgery, including SLNB, in patients with DCIS undergoing TM. Thus, considering quality of life, there is a need for research on the role of axillary surgery from a clinical perspective. Therefore, we aimed to explore the clinicopathological factors and outcomes associated with axillary surgery in patients with a final diagnosis of pure DCIS who underwent either BCS or TM, to evaluate the role of axillary surgery, including SLNB, in the treatment of TM.

METHODS

Data collection

We used data approved by the Korean Breast Cancer Society's registration system (KBCR), a dataset that has accumulated breast cancer cases registered voluntarily by breast surgeons nationwide [20]. Information regarding the cause and date of death was obtained via the complete death statistics updated until 2014 through linkages with the Korean Central Cancer Registry under the Ministry of Health and Welfare and the Korean National Statistical Office. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Daejeon St. Mary's

Hospital (No. DC22ZASI0036). The requirement for informed consent was waived by the IRB owing to the retrospective nature of the study.

Patients and clinicopathological variables

We retrospectively analyzed large-scale data from the KBCR database, focusing on patients diagnosed with pure DCIS and excluding patients with residual DCIS after neoadjuvant chemotherapy. Patients who underwent surgery were categorized into two groups: BCS and TM. Patients were further categorized into surgery and non-surgery groups according to their axillary surgery status. The analysis compared clinicopathological factors and outcomes according to axillary surgery status between the BCS and TM groups. The fundamental clinical characteristics of the patients included the year of surgery; age; body mass index (BMI); axillary surgery status; tumor size; multiplicity and location of tumors; palpability; clinical lymph node status; nuclear grade; immunohistochemistry results for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67; and radiation therapy. Continuous variables included year of surgery, age, BMI, tumor size, and Ki-67 index. Age was categorized into 5-year intervals for individuals between 20 and 79 years, with those under 20 and 80 years or over grouped separately. BMI was rounded off to the nearest whole number, and values between 18 and 30 were categorized individually in ascending order, whereas values under 17 and 31 or over were grouped separately. Tumor size was categorized in 0.5-cm increments, with sizes exceeding 5.0 cm grouped together. Ki-67 was categorized in 10% intervals because of its sharp increase in case numbers at every 10%.

Statistical analysis

For both the BCS and TM groups, we conducted comparative analyses of clinicopathological variables according to the performance of axillary surgery using Student's *t*-test and χ^2 test. Furthermore, logistic regression analysis was used to compare the clinicopathological factors associated with axillary surgery between the BCS and TM groups. Clinicopathological factors associated with axillary surgery were analyzed using univariate logistic regression analysis to calculate odds ratios, and multivariate analysis was used to identify factors influencing the decision to perform axillary surgery. In the axillary surgery group, clinicopathological factors associated with lymph node metastasis were analyzed using the same logistic regression analysis method. Radiation therapy was excluded from the analysis of clinicopathological factors associated with axillary surgery performance or lymph node metastasis because it is considered an adjuvant therapy. The change in the axillary surgery rate according to the increase or decrease in continuous variables was represented by the slope using a binomial distribution and linear regression analysis, and the influence of the variables was expressed by the coefficient of determination (R^2). Survival analysis was conducted separately for the BCS and TM groups based on breast cancer-specific survival (BCSS) and overall survival (OS). The 5-year survival rates were compared based on the performance of axillary surgery using the Kaplan–Meier method, and the Cox proportional hazards model was used to analyze the hazard ratio (HR) of the axillary surgery group compared with the no axillary surgery group. All statistical analyses were performed using the IBM SPSS Statistics ver. 26.0 (IBM Corp., Armonk, USA), with statistical significance defined as $p < 0.05$.

RESULTS

Clinical characteristics

Among 18,196 patients who underwent surgery for DCIS between 1981 and 2022, 11,872 underwent BCS and 6,324 underwent TM. Axillary surgery was conducted in 55.4% and 81.6% of patients who underwent BCS and TM, respectively. Factors associated with a higher rate of axillary surgery in the BCS group included age ≥ 50 years, tumor size > 1 cm, single tumor, upper tumor location, palpable mass, nuclear grade 3, ER negative, PR negative, HER2 positive, Ki-67 ≥ 20%, and underwent radiation therapy. In the TM group, factors included tumor size > 2 cm, clinical lymph node positivity, PR negativity, HER2 positivity, and did not undergo radiation therapy. In terms of continuous variables for BCS, the mean age, tumor size, and Ki-67 values of the axillary surgery group were significantly higher than those of the non-surgery group. However, for the TM, only the mean tumor size was significantly larger in the axillary surgery group (**Table 1**).

Correlation of axillary surgery performance rate with continuous variables

In the linear regression analysis of continuous variables, the axillary surgery rate in DCIS demonstrated a decreasing trend with year of surgery in BCS (−0.009; $R^2 = 0.287$; 95% confidence interval [CI], −0.014 – −0.004; $p = 0.001$), while it exhibited an increasing pattern with a large tumor size (0.017; $R^2 = 0.599$; 95% CI, 0.007 – 0.028; $p = 0.005$). Conversely, in the TM, the axillary surgery rate increased with the year of surgery (0.009; $R^2 = 0.332$; 95% CI, 0.004–0.013; $p < 0.001$) and with a large tumor size (0.018; $R^2 = 0.922$; 95% CI, 0.014–0.022; $p < 0.001$). Age, BMI, and Ki-67 index did not reveal significant changes in either the BCS or TM groups (**Figure 1**).

Factors associated with the performance of axillary surgery and axillary lymph node metastasis

In DCIS, the clinicopathological factors correlated with undergoing axillary surgery in BCS were tumor size > 2.0 cm and ≤ 5.0 cm (odds ratio [OR], 1.350; $p = 0.017$), palpable mass (OR, 1.894; $p < 0.001$), clinically lymph node positive (OR, 3.857; $p = 0.007$), nuclear grade 3 (OR, 1.359; $p = 0.026$), and HER2 positive (OR, 1.339; $p = 0.034$). In TM, axillary surgery can be performed as the tumor size increased (> 2.0 cm and ≤ 5.0 cm [OR, 1.631; $p = 0.002$], > 5.0 cm [OR, 2.180; $p < 0.001$]) and when the tumor was non-palpable (OR, 0.657; $p < 0.001$) (**Table 2**). When axillary surgery was conducted, the lymph node metastasis rates in the BCS and TM groups were 0.19% and 0.24%, respectively. In the BCS group, clinical lymph node status (OR, 11.101; $p = 0.003$) was associated with lymph node metastasis, whereas in the TM group, no significant differences were observed in any factor (**Supplementary Figure 1**).

Prognosis

The median follow-up period was 53 months for BCS (range: 0–292 months) and 73 months for TM (range: 0–404 months). The 5-year survival rates based on axillary surgery were as follows: for BCSS, BCS (no axillary surgery; 100.0%, SLNB; 99.8%, $p = 0.360$) and TM (no axillary surgery; 99.8%, SLNB; 99.8%, $p = 0.697$); for OS, BCS (no axillary surgery; 99.1%, SLNB; 98.9%, $p = 0.706$) and TM (no axillary surgery; 98.6%, SLNB; 98.9%, $p = 0.431$) (**Figure 2**). Regardless of the presence or absence of adjuvant radiation therapy, the 5-year survival rates based on axillary surgery did not show significant differences in both the BCS and TM groups (**Supplementary Figure 2**). When adjusting for the influence of each factor on Cox proportional hazard ratios, BCS (BCSS [HR, 2.656; $p = 0.386$], OS [HR, 1.006; $p = 0.984$]) and TM (BCSS [HR, 0.770; $p = 0.679$], OS [HR, 0.835; $p = 0.454$]) showed no significant differences in survival based on axillary surgery (**Figure 3**).

Table 1. Clinicopathological characteristics of patients with ductal carcinoma *in situ*

Factors	Breast-conserving surgery (n = 11,872)			Total mastectomy (n = 6,324)		
	No axillary surgery	Axillary surgery	*p*-value	No axillary surgery	Axillary surgery	*p*-value
Total patients	5,300 (100.0)	6,572 (100.0)		1,164 (100.0)	5,160 (100.0)	
Age (yr)	49.64 ± 10.48	50.17 ± 9.99	0.005	49.77 ± 10.34	50.22 ± 10.70	0.195
< 50	2,890 (54.5)	3,404 (51.8)	0.003	646 (55.5)	2,758 (53.4)	0.205
≥ 50	2,410 (45.5)	3,168 (48.2)		518 (44.5)	2,402 (46.6)	
BMI (kg/m²)	23.27 ± 6.15	23.23 ± 4.75	0.718	23.10 ± 3.16	23.14 ± 3.30	0.758
< 25	3,057 (57.7)	3,945 (60.0)	0.001	712 (61.2)	3,153 (61.1)	0.998
≥ 25	1,045 (19.7)	1,319 (20.1)		229 (19.7)	1,019 (19.7)	
Unknown	1,198 (22.6)	1,308 (19.9)		223 (19.2)	988 (19.1)	
Tumor size (cm)	1.56 ± 2.10	1.97 ± 6.19	< 0.001	2.60 ± 1.99	3.46 ± 2.50	< 0.001
≤ 1.0	2,007 (37.9)	1,780 (27.1)	< 0.001	217 (18.6)	592 (11.5)	< 0.001
> 1.0 and ≤ 2.0	1,223 (23.1)	1,677 (25.5)		258 (22.2)	789 (15.3)	
> 2.0 and ≤ 5.0	886 (16.7)	1,427 (21.7)		316 (27.1)	1,743 (33.8)	
> 5.0	88 (1.7)	207 (3.1)		104 (8.9)	823 (15.9)	
Unknown	1,096 (20.7)	1,481 (22.5)		269 (23.1)	1,213 (23.5)	
Multiplicity			0.004			< 0.001
Single	3,612 (68.2)	4,649 (70.7)		869 (74.7)	3,402 (65.9)	
Multiple	258 (4.9)	326 (5.0)		144 (12.4)	505 (9.8)	
Unknown	1,430 (27.0)	1,597 (24.3)		151 (13.0)	1,253 (24.3)	
Location			< 0.001			< 0.001
Upper-outer	1,748 (33.0)	2,361 (35.9)		435 (37.4)	1,517 (29.4)	
Lower-outer	455 (8.6)	572 (8.7)		115 (9.9)	402 (7.8)	
Upper-inner	655 (12.4)	879 (13.4)		159 (13.7)	574 (11.1)	
Lower-inner	260 (4.9)	285 (4.3)		58 (5.0)	205 (4.0)	
Central	314 (5.9)	325 (4.9)		180 (15.5)	512 (9.9)	
Unknown	1,868 (35.2)	2,150 (32.7)		217 (18.6)	1,950 (37.8)	
Palpability			< 0.001			< 0.001
Non-palpable	2,276 (42.9)	2,526 (38.4)		441 (37.9)	1,712 (33.2)	
Palpable	974 (18.4)	1,609 (24.5)		436 (37.5)	1,457 (28.2)	
Unknown	2,050 (38.7)	2,437 (37.1)		287 (24.7)	1,991 (38.6)	
Clinical LN status			< 0.001			< 0.001
Negative	3,089 (58.3)	4,076 (62.0)		841 (72.3)	3,225 (62.5)	
Positive	30 (0.6)	125 (1.9)		27 (2.3)	142 (2.8)	
Unknown	2,181 (41.2)	2,371 (36.1)		296 (25.4)	1,793 (34.7)	
Nuclear grade			< 0.001			0.007
Grade 1 or 2	2,684 (50.6)	2,755 (41.9)		368 (31.6)	1,750 (33.9)	
Grade 3	614 (11.6)	1,099 (16.7)		193 (16.6)	991 (19.2)	
Unknown	2,002 (37.8)	2,718 (41.4)		603 (51.8)	2,419 (46.9)	
ER			< 0.001			< 0.001
Negative	675 (12.7)	1,289 (19.6)		259 (22.3)	1,385 (26.8)	
Positive	4,239 (80.0)	4,971 (75.6)		753 (64.7)	3,459 (67.0)	
Unknown	386 (7.3)	312 (4.7)		152 (13.1)	316 (6.1)	
PR			< 0.001			< 0.001
Negative	992 (18.7)	1,743 (26.5)		311 (26.7)	1,722 (33.4)	
Positive	3,883 (73.3)	4,505 (68.5)		701 (60.2)	3,103 (60.1)	
Unknown	425 (8.0)	324 (4.9)		152 (13.1)	335 (6.5)	
HER2			< 0.001			< 0.001
Negative	3,071 (57.9)	3,347 (50.9)		497 (42.7)	2,128 (41.2)	
Positive	788 (14.9)	1,486 (22.6)		260 (22.3)	1,588 (30.8)	
Unknown	1,441 (27.2)	1,739 (26.5)		407 (35.0)	1,444 (28.0)	
Ki-67 (%)	9.41 ± 12.19	11.37 ± 13.02	< 0.001	11.32 ± 11.70	12.08 ± 12.72	0.220
< 20	2,861 (54.0)	3,346 (50.9)	< 0.001	371 (31.9)	2,277 (44.1)	< 0.001
≥ 20	567 (10.7)	940 (14.3)		105 (9.0)	766 (14.8)	
Unknown	1,872 (35.3)	2,286 (34.8)		688 (59.1)	2,117 (41.0)	
Radiation therapy			< 0.001			< 0.001
No	737 (13.9)	634 (9.6)		835 (71.7)	4,268 (82.7)	
Yes	4,070 (76.8)	5,247 (79.8)		108 (9.3)	242 (4.7)	
Unknown	493 (9.3)	691 (10.5)		221 (19.0)	650 (12.6)	

Values are presented as means ± standard deviations or numbers (%).
BMI = body mass index; LN = lymph node; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth receptor 2.

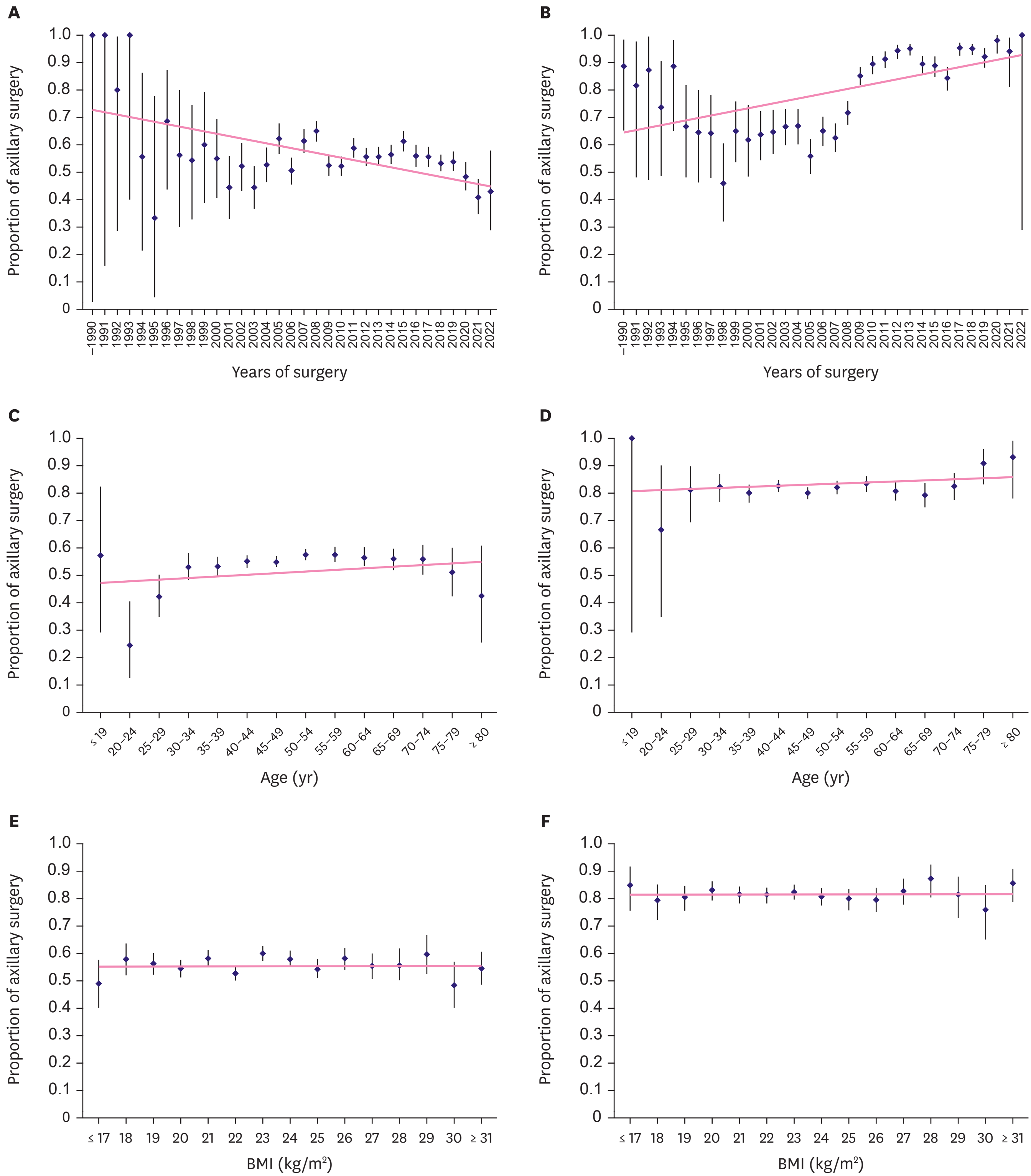

Figure 1. Linear regression models demonstrate the correlation between the proportion of axillary surgery and continuous variables, including (A, B) year of surgery, (C, D) age, (E, F) body mass index, (G, H) tumor size, and (I, J) Ki-67 status in breast-conserving surgery (A, C, E, G, I) and total mastectomy (B, D, F, H, J) respectively. The black dots and lines reflect the proportion of axillary surgery for each variable, along with their 95% confidence intervals. The slopes of the colored lines indicate the correlation between the proportion of axillary surgery and the continuous variables. (continued to the next page)
BMI = body mass index.

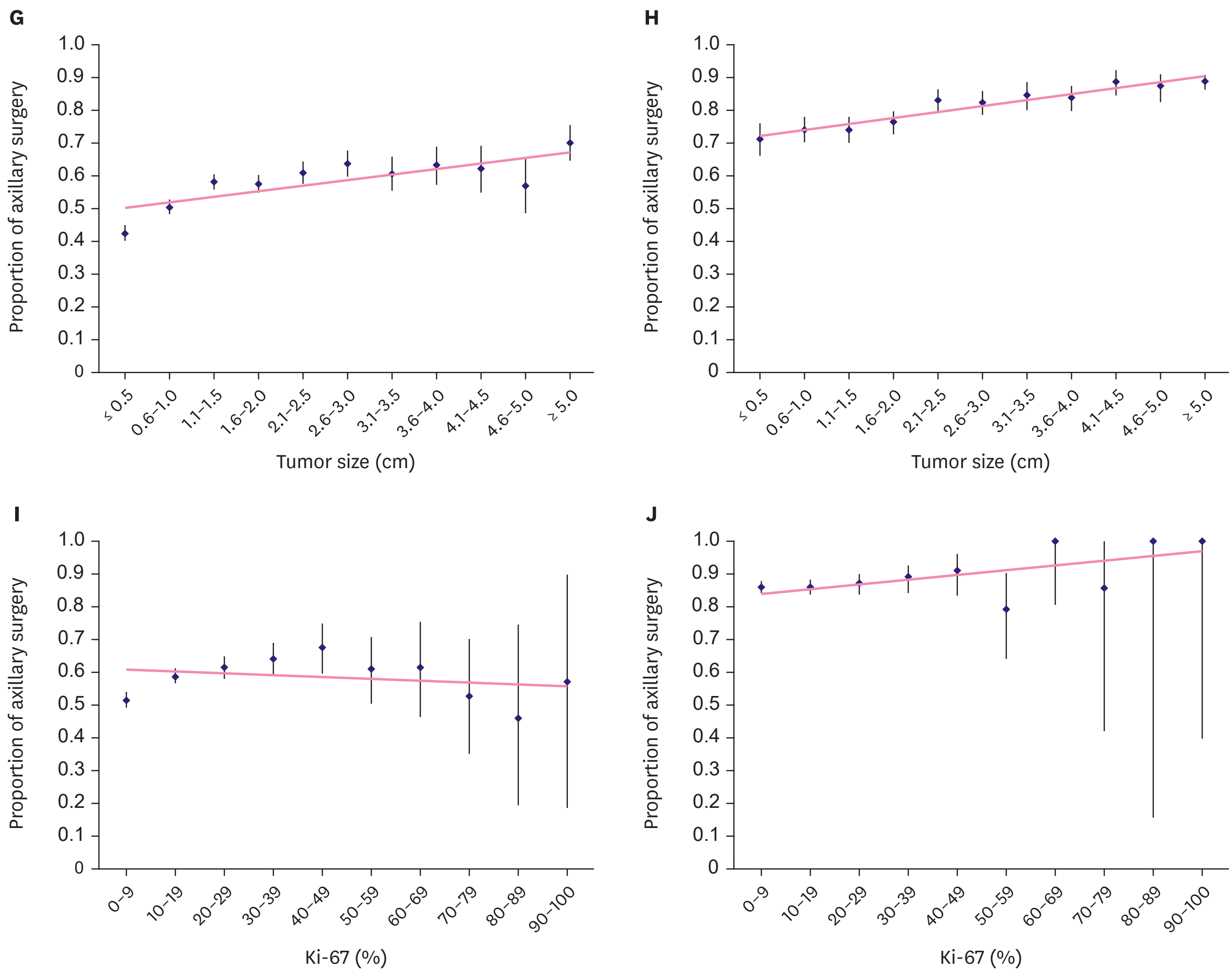

Figure 1. (Continued) Linear regression models demonstrate the correlation between the proportion of axillary surgery and continuous variables, including (A, B) year of surgery, (C, D) age, (E, F) body mass index, (G, H) tumor size, and (I, J) Ki-67 status in breast-conserving surgery (A, C, E, G, I) and total mastectomy (B, D, F, H, J) respectively. The black dots and lines reflect the proportion of axillary surgery for each variable, along with their 95% confidence intervals. The slopes of the colored lines indicate the correlation between the proportion of axillary surgery and the continuous variables.
BMI = body mass index.

DISCUSSION

In DCIS, axillary surgery is not recommended in BCS; however, this study suggests a tendency to perform axillary surgery based on preoperative clinical factors, such as tumor size and clinical lymph node status, which are considered high-risk factors for diagnostic upgrades. Conversely, in TM, significant factors were fewer than in BCS, and there was a tendency to perform axillary surgery in clinical categories that were different from those in BCS, such as non-palpable tumors. A bias exists resulting from the fact that in accordance with the ASCO and NCCN guidelines, axillary surgery is performed in most TM cases rather than BCS. However, for both BCS and TM, a large tumor size was consistently associated with a higher rate of axillary surgery. Diagnostic upgrade to invasion can be an important factor affecting the axillary surgery rate in patients with DCIS. Although we underscored on DCIS based on the final diagnosis, our results indicate that large DCIS lesions are more likely to

Table 2. Performance of axillary surgery according to the factors

Factors	Breast-conserving surgery				Total mastectomy			
	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age (yr)								
< 50	1.000		1.000		1.000			
≥ 50	1.116 (1.038–1.200)	0.003	0.974 (0.797–1.191)	0.800	1.086 (0.956–1.234)	0.205		
BMI (kg/m²)								
< 25	1.000				1.000			
≥ 25	0.978 (0.890–1.074)	0.644			1.005 (0.852–1.185)	0.954		
Tumor size (cm)								
≤ 1.0	1.000		1.000		1.000		1.000	
> 1.0 and ≤ 2.0	1.546 (1.402–1.704)	< 0.001	1.235 (0.982–1.553)	0.071	1.121 (0.909–1.382)	0.286	0.881 (0.628–1.236)	0.462
> 2.0 and ≤ 5.0	1.816 (1.634–2.018)	< 0.001	1.350 (1.054–1.728)	0.017	2.022 (1.661–2.460)	< 0.001	1.631 (1.188–2.240)	0.002
> 5.0	2.652 (2.050–3.431)	< 0.001	1.942 (0.923–4.088)	0.081	2.901 (2.244–3.749)	< 0.001	2.180 (1.473–3.228)	< 0.001
Multiplicity								
Single	1.000				1.000			
Multiple	0.982 (0.829–1.162)	0.831			0.896 (0.734–1.094)	0.280		
Location								
Upper-outer	1.000		1.000		1.000		1.000	
Lower-outer	0.931 (0.811–1.068)	0.307	0.745 (0.552–1.007)	0.055	1.002 (0.794–1.265)	0.984	1.162 (0.819–1.649)	0.401
Upper-inner	0.994 (0.882–1.119)	0.915	0.849 (0.657–1.096)	0.209	1.035 (0.843–1.271)	0.741	1.161 (0.850–1.586)	0.349
Lower-inner	0.812 (0.678–0.971)	0.022	0.813 (0.550–1.202)	0.299	1.014 (0.743–1.382)	0.932	1.167 (0.737–1.849)	0.509
Central	0.766 (0.648–0.906)	0.002	0.759 (0.541–1.064)	0.109	0.816 (0.667–0.997)	0.046	1.165 (0.842–1.610)	0.356
Palpability								
Non-palpable	1.000		1.000		1.000		1.000	
Palpable	1.488 (1.350–1.641)	< 0.001	1.894 (1.509–2.377)	< 0.001	0.861 (0.741–0.999)	0.049	0.657 (0.526–0.822)	< 0.001
Clinical LN status								
Negative	1.000		1.000		1.000			
Positive	3.158 (2.114–4.716)	< 0.001	3.857 (1.441–10.321)	0.007	1.371 (0.903–2.084)	0.139		
Nuclear grade								
Grade 1 or 2	1.000		1.000		1.000			
Grade 3	1.744 (1.559–1.951)	< 0.001	1.359 (1.038–1.781)	0.026	1.080 (0.892–1.307)	0.431		
ER								
Negative	1.000		1.000		1.000			
Positive	0.614 (0.555–0.680)	< 0.001	0.912 (0.639–1.303)	0.614	0.859 (0.736–1.002)	0.054		
PR								
Negative	1.000		1.000		1.000		1.000	
Positive	0.660 (0.604–0.722)	< 0.001	1.251 (0.893–1.752)	0.193	0.799 (0.691–0.925)	0.003	0.962 (0.741–1.249)	0.771
HER2								
Negative	1.000		1.000		1.000		1.000	
Positive	1.730 (1.567–1.911)	< 0.001	1.339 (1.022–1.754)	0.034	1.426 (1.211–1.680)	< 0.001	1.218 (0.940–1.578)	0.136
Ki-67 (%)								
< 20	1.000		1.000		1.000			
≥ 20	1.418 (1.263–1.591)	< 0.001	1.084 (0.846–1.389)	0.522	1.189 (0.943–1.498)	0.144		

OR = odds ratio; CI = confidence interval; BMI = body mass index; LN = lymph node; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth receptor 2.

harbor invasive carcinomas. Chiu et al. [21] reported in a meta-analysis of 13 studies that the upgrade of DCIS had a significant difference, with 14.7% for tumor size < 2.0 cm and 30.0% for tumor size ≥ 2.0 cm. Tanaka et al. [22] reported that a tumor size > 20 mm on magnetic resonance imaging was an independent predictor of invasive ductal carcinoma in patients diagnosed with DCIS before surgery. El Hage Chehade et al. [23] showed in a meta-analysis of 48 studies on SLNB in DCIS that high-grade DCIS > 20 mm was the only factor associated with the performance of SLNB. Moreover, Dutch guidelines recommend conducting SLNB in cases of high-risk invasion, irrespective of the selected breast surgical method. High-risk features included tumor size exceeding 2.5 cm, grade 3 DCIS, extensive calcifications, and age < 55 years [13].

https://doi.org/10.4048/jbc.2023.0221

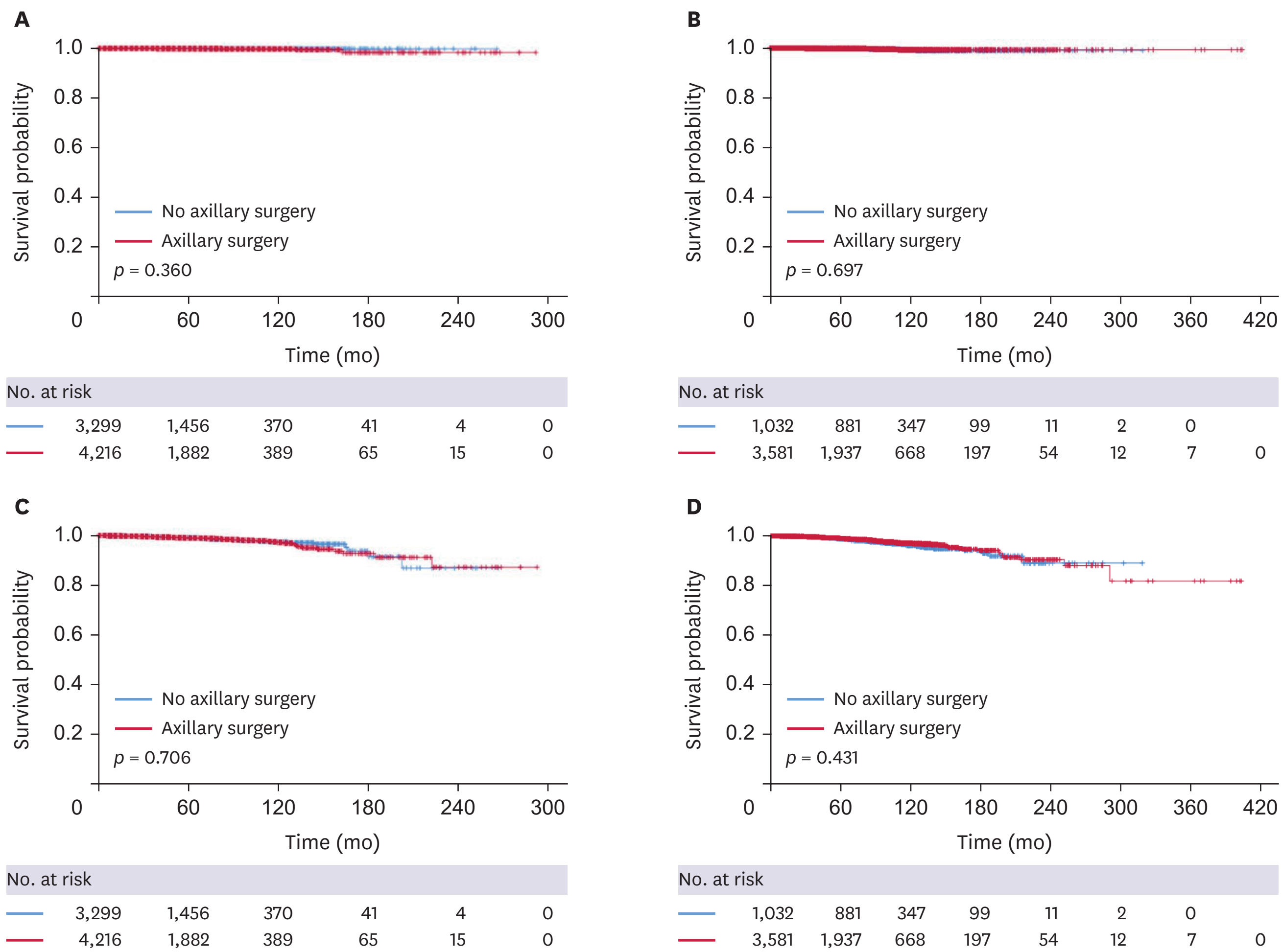

Figure 2. Survival curves according to axillary surgery in ductal carcinoma *in situ*. (A) Breast cancer-specific survival in breast-conserving surgery, (B) breast cancer-specific survival in total mastectomy, (C) overall survival in breast-conserving surgery, and (D) overall survival in total mastectomy.

In cases where axillary surgery was performed in the TM, the absolute proportion of patients with confirmed metastasis was higher than that in patients who underwent BCS. However, this difference was not statistically significant owing to the small sample size. Clinical lymph node status was the only factor found to have an impact on BCS, whereas no factors associated with metastasis were noted for TM. In previous studies involving the histological examination of axillary lymph nodes in patients with breast cancer [24,25] and predictive models for diagnostic upgrading of DCIS [26], clinically suspicious axillary lymph nodes were reported as important factors. Thus, clinical lymph node status can also be considered a factor that should be considered when deciding on axillary surgery in cases of DCIS.

In this study, no significant difference was found in the survival rates based on axillary surgery for either BCS or TM. Axillary surgery does not affect the survival of patients with DCIS. However, research on the impact of axillary surgery on survival in DCIS remains limited [27,28], and axillary surgery for DCIS continues to be performed according to current guidelines. This indicates that the role of axillary surgery as a nodal evaluation is emphasized rather than as a therapeutic intervention owing to the trend towards the de-escalation of axillary surgery and adjuvant therapy development [29].

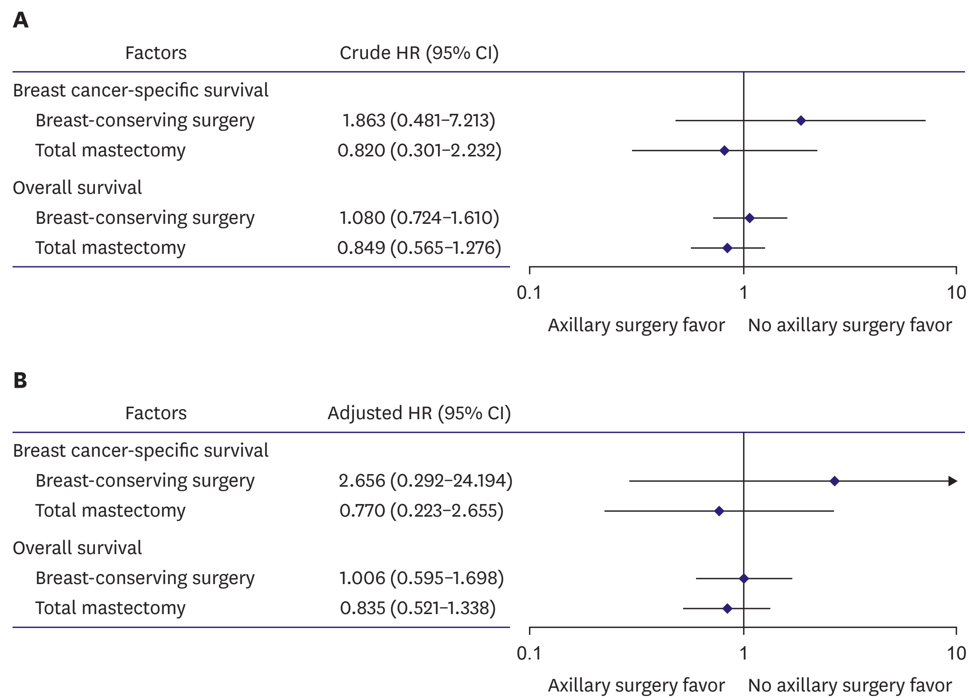

Figure 3. Prognosis according to axillary surgery in ductal carcinoma *in situ*. (A) Univariate analysis and (B) multivariate analysis.
HR = hazard ratio; CI = confidence interval.

Axillary surgery for DCIS is considered due to the possibility of diagnostic upgrade and subsequent risk of axillary lymph node metastasis after surgery. The rates of diagnostic upgrading based on breast surgical methods have been reported to be similar in various studies, ranging from 10.9% to 24.0% for BCS and 13.7% to 30.4% for TM [11,30]. However, Shin et al. [9] reported that, among patients diagnosed with DCIS who underwent TM, 2.7% (4/148) had sentinel lymph node (SLN) metastases, all of which were diagnostic upgrades. Conversely, no SLN metastases were noted in patients who underwent BCS (0/54). Based on this finding, the authors suggested the necessity for axillary surgery in patients with TM. Another reason is that the lymphatic drainage pathway may be compromised during breast surgery, rendering an accurate delayed SLNB difficult. Feldman et al. [31] reported a relatively high false-negative rate with SLNB, especially when an excisional biopsy was performed for breast cancer, particularly in cases with wider excision areas. This can be considered a fundamental reason for axillary surgery in patients with DCIS. However, subsequent studies have refuted these existing views. Poodt et al. [32] conducted a systematic review of repeat SLNB in patients with ipsilateral breast tumor recurrence. They reported that the technical success rate of repeat SLNB, although not statistically significant, was higher in the primary mastectomy group (67.7%) than in the primary lumpectomy group (59.7%) ($p = 0.050$) and significantly higher in the primary no-axillary procedure group (84.9%) than in the primary SLNB group (75.7%) ($p < 0.001$). Karakatsanis et al. [33] reported that using nanoparticles to mark the SLN allows for accurate delayed SLNB, if warranted. Hence, axillary surgery in DCIS may be necessary in cases of diagnostic upgrading; however, unnecessary axillary surgery can be avoided by delaying SLNB after the final diagnosis. Furthermore, prospective randomized clinical trials such as the SOUND, INSEMA, and BOOG 2013-08 trials have omitted SLNB for invasive breast cancer [29,34]. The recently published SOUND trial revealed no difference in the 5-year distant disease-free survival, disease-free survival, and OS rates, indicating that omitting

SLNB in ultrasonographic lymph node-negative, small invasive breast cancer does not affect survival rates. Moreover, even when patients with pathological axillary lymph node metastases were included in the SLNB group, no differences were noted in the survival outcomes compared with the no axillary surgery group [35]. This indicates that even when there is evidence of low-burden pathological axillary lymph node metastases, the impact on survival is negligible because of other protective adjuvant therapies, such as radiation or antiestrogen therapy, which improve survival outcomes. Therefore, in some DCIS cases, axillary surgery, including SLNB, can be omitted if proper adjuvant therapy is administered, even if suspicious diagnostic upstaging or pathological axillary lymph node metastases are evident.

This study has several limitations. First, it was based on a retrospective data analysis, which may have introduced selection bias due to data omissions for some factors. Additionally, the analysis of survival rates only includes mortality data until 2014 due to the Personal Information Protection Act and thus does not reflect recent survival data. The study is also limited in its analysis of upgraded stages because it only included the final diagnosed DCIS data from registration. Moreover, the tumor size variable was based on the pathological tumor size and was associated with axillary surgery. However, because of the significant role of the clinical tumor size in the selection of the surgical method during DCIS treatment, accurately explaining the relationship between tumor size and axillary surgery in the actual treatment process is challenging. Moreover, there are various reasons for performing TM beyond clinical indications, including cosmetic purposes and patient preference. However, these factors were not reflected in the data, which could have led to the heterogeneity in the clinical characteristics of axillary surgery for TM. Nevertheless, this study used large-scale data from multiple institutions, which allowed for a more objective analysis. By directly comparing the clinical characteristics and survival rates of axillary surgery between BCS and TM, we provided insights into the patterns of axillary surgery according to the breast surgical methods.

This study confirmed that no difference was found in the prognosis based on the performance of axillary surgery in patients with a final diagnosis of pure DCIS, regardless of whether they underwent BCS or TM. Furthermore, regardless of the breast surgical method, axillary surgery, including SLNB, should be considered for high-risk patients, such as those with large tumors. This approach may reduce unnecessary axillary surgery and improve the patients' quality of life.

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SUPPLEMENTARY MATERIALS

Supplementary Figure 1

Factors associated with axillary lymph node metastasis in (A) breast-conserving surgery and (B) total mastectomy.

Supplementary Figure 2

Survival curves according to axillary surgery in ductal carcinoma *in situ* with or without adjuvant radiation therapy. (A-C) Breast cancer-specific survival in breast-conserving surgery

(A) without or (B) with adjuvant radiation therapy and in total mastectomy (C) without adjuvant radiation therapy; (D-G) overall survival in breast-conserving surgery (D) without or (E) with adjuvant radiation therapy and in total mastectomy (F) without or (G) with adjuvant radiation therapy. The survival curve of breast cancer-specific survival in total mastectomy with adjuvant radiation therapy could not be estimated.

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