Comparison of Survival Outcomes for Axillary Surgery Extent Based on Intraoperative Sentinel Lymph Node Biopsy Result After Neoadjuvant Chemotherapy for Breast Cancer

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Abstract

Purpose

To investigate the survival difference between limited axillary surgery and full axillary lymph node dissection (ALND) in patients with 1-3 positive sentinel lymph node biopsies (SLNBs) after neoadjuvant chemotherapy (NAC).

Method

We retrospectively analyzed data from 676 patients who underwent surgery between 2007 and 2017 with cT1-4, cN0-3, cM0 breast cancer at the time of diagnosis and 1-3 positive SLNBs after NAC. The patients received either SLNB only or completed level I or II ALND based on SLNB results. After propensity score matching, 483 patients who had undergone SLNB only (n=188) and ALND (n=295) were included. We examined overall survival, axillary recurrence-free survival, regional recurrence-free survival, and distant metastasis-free survival and compared them between the subgroups.

Result

At a median follow-up of 59.4 months, no significant statistical difference was observed in overall survival, axillary recurrence-free survival, regional recurrence-free survival, and distant metastasis-free survival between SLNB only and ALND. No significant differences were observed in the 5-year axillary recurrence-free survival (93.1% vs. 94.0%, hazard ratio [HR]=0.94, 95% confidence interval [CI]=0.43-2.05, p=0.876) and 5-year overall survival (97.7% vs. 97.3%, HR=1.65, 95% CI=0.58-4.65, p=0.347) between the two groups.

Conclusion

Our analysis suggests that SLNB alone may be a possible option for patients with 1-3 sentinel node-positive breast cancer following NAC without significant compromise of recurrence or overall survival.

Introduction

Many breast cancer patients with clinically node-positive biopsy receive preoperative chemotherapy for a possible reduction of tumor burden and surgical extent. Neoadjuvant chemotherapy (NAC) reduces the need for axillary lymph node dissection (ALND), and sentinel lymph node biopsy (SLNB) is an appropriate method of determining nodal status after NAC. [1–3] The presence of axillary node metastasis during SLNB is an important factor in making treatment decisions in breast cancer.

For primary breast cancer patients without NAC, according to the recent National Comprehensive Cancer Network (NCCN) guidelines, no further axillary surgery for positive sentinel lymph node (SLN) can be considered if micro-metastasis is seen in SLN or if the patient meets all of the following criteria from the ACOSOG Z0011 trial: T1 or T2 tumor, 1 or 2 positive SLNs, breast-conserving surgery and planned whole breast radiation therapy, and no preoperative chemotherapy.
If any of the above criteria are not met, the NCCN panel recommends level I or II axillary dissection. [4]

Traditionally, for patients who presented with node-positive breast cancer after NAC, ALND has been the standard surgical method of choice. To avoid well-known adverse effects of ALND, including lymphedema, there has been a shift toward less extensive dissection recently.

According to Almahariq et al., slightly over a quarter of patients with ypN1 breast cancer did not undergo an ALND in the National Cancer Data Base-affiliated institutions in 2014.

After the ACOSOG Z0011 results were published, there has been a clear trend of SLNB for ypN1 patients. [5] Kantor et al. reported that 26% of patients who were ypN1 on final pathology underwent SLND only in 2013 based on the National Cancer Data Base study of 12,063 women.[6]

Our institutional practice patterns have also evolved to incorporate SLNB as the initial surgical method of choice for the axilla after NAC unless the patient has definitive substantial axillary disease burden remaining despite NAC.

However, the safety of SLNB alone in positive nodal disease after preoperative chemotherapy is currently unknown. It is also an investigation area to make an optimal surgical decision on whether to proceed to completion of ALND or only SLNB after 1–3 positive SLNs are identified during surgery. The omission of ALND has increased gradually during recent years in our institution's practice pattern in this setting. Adjuvant radiation and endocrine therapy were provided if a patient's status was found to be appropriate for these treatments.

We analyzed these patient's data obtained from our practice and compared recurrence and survival outcomes between the subgroups.

Material And Methods

Patients

We reviewed data from 717 patients who underwent surgery between January 2007 and December 2017 with cT1-4, cN0-3, cM0 breast cancer and 1–3 SLNs positive after preoperative chemotherapy.
We excluded patients with bilateral breast cancer, those with possible M1 status at the time of initial chemotherapy, those diagnosed with cancer of another origin other than breast during the follow-up, and those lost to follow-up within 6 months after surgery. Finally, a total of 676 patients were included for further analysis. All surgical axillary staging was performed after the completion of NAC. The patients received either SLNB only or completion of level I or II ALND after SLNB. The median follow-up period was 59.4 (range 7.3–153) months after surgery.

All patient information and tumor characteristics were retrieved from our prospectively collected database. The following clinical and pathologic data were obtained: age at diagnosis, tumor grade, hormone receptor and HER2 receptor status, initial clinical stage, pathologic stage, number of lymph nodes that are positive for malignancy, surgical methods, types of adjuvant treatment modalities, type of recurrence, and follow-up period. We analyzed axillary recurrence-free survival, regional recurrence-free survival, distant metastasis-free survival, and overall survival and compared them between the groups.

The pathologic stage classification was based on the definitions presented in the 8th edition of the American Joint Committee on Cancer staging system.
This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, South Korea (20171341). Because the study was based on retrospective clinical data, the need for informed consent was waived.

Adjuvant radiation therapy was administered to patients with clinical or pathological stage 3 disease regardless of axillary nodal status after surgery. Those included were all patients who underwent breast-conserving surgery and high-risk patients who underwent mastectomy. Also, adjuvant endocrine therapy was administered to patients with positive estrogen or progesterone receptor status. Patients with HER2-positive status were treated with standard target therapy before and after surgery.

Statistical analysis

The primary endpoint was the time to disease recurrence as the first event, and we classified it based on the recurrence site. Axillary recurrence-free survival was defined as the time from the date of the surgery to the date of an initial ipsilateral axillary recurrence, which was proven either radiologically or pathologically. Regional recurrence-free survival was defined as the time from the date of the surgery to the date of recurrence at the ipsilateral axillary, supraclavicular, infraclavicular, and internal mammary lymph node. Distant metastasis-free survival was defined as the interval from operation to the time of the first detection of distant metastasis, while overall survival was defined as the interval from the initial surgery to the time of death. We analyzed the axillary recurrence rate separately from regional recurrence to investigate the difference in tumor relapse in the axilla between the groups.

Considering the retrospective nature of this study, we stratified our patients' data with propensity score matching (PSM) between the SLNB only and ALND groups. The baseline variables for the matching were age, tumor grade, hormonal and HER2 receptors status, initial clinical T and N stage, number of metastatic nodes during SNB, and adjuvant endocrine therapy. We stratified our data specifically for both radiation and breast surgery type, and we performed PSM within each subgroup. A 1:1 matching was done for 81 pairs, and an additional 1:2 matching was performed for 107 pairs to recruit as much data as possible for analysis. We used the Pearson chi-square test and conditional logistic regression method to compare the results among these groups.

We performed statistical analysis under unadjusted, multivariable-adjusted, and propensity score-matched conditions after sorting the patient's data according to the types of recurrence and survival.
We used Cox proportional hazards model with robust standard errors to account for clustering in matched pairs. The Kaplan-Meier method was utilized to visualize survival graphs before and after patient data matching. All statistical analyses were conducted with SPSS statistics version 23.0 (IBM Corp., Armonk, USA).

Results

Baseline characteristics

The median age was 47.0 (range 24–80) years. Among 676 patients, 201 (29.7%) underwent SLNB only and 475 (70.3%) underwent ALND. Detailed baseline characteristics for the unmatched and matched cohorts are listed in Table 1. Before matching, significant heterogeneity was observed between the two groups. Patients in the SLNB group tended to show more favorable tumor grade, lower clinical T stage, and fewer positive sentinel nodes than those in the ALND group. It was apparent that patients with less tumor burden or more favorable tumor biology had received SLNB more frequently. There were no significant differences in all of the baseline characteristics after matching.

Table 1
Baseline patient characteristics

	Before PSM			After PSM		
	SLNB only	ALND	P-value†	SLNB only	ALND	P-value‡
Number of patients	201	475		188	295	
Age at diagnosis			0.655			0.6102
< 50 years	131 (65.2)	301 (63.4)		126 (67.0)	201 (68.1)	
≥ 50 years	70 (34.8)	174 (36.6)		62 (33.0)	94 (31.9)	
Nuclear grade			0.0031			0.7645
G1/2	184 (91.5)	393 (82.7)		172 (91.5)	267 (90.5)	
G3	17 (8.5)	82 (17.3)		16 (8.5)	28 (9.5)	
HER2 status			0.1054			0.6698
negative	168 (83.6)	371 (78.1)		156 (83.0)	244 (82.7)	
positive	33 (16.4)	104 (21.9)		32 (17.0)	51 (17.3)	
Hormone receptor			0.6768			0.3763
negative	40 (19.9)	88 (18.5)		32 (17.0)	44 (14.9)	
positive	161 (80.1)	387 (81.5)		156 (83.0)	251 (85.1)	
Clinical T stage			0.0198			0.8147
T1	33 (16.4)	43 (9.1)		26 (13.8)	31 (10.5)	
T2	123 (61.2)	289 (60.8)		118 (62.8)	178 (60.3)	
T3	40 (19.9)	128 (26.9)		39 (20.7)	76 (25.8)	
T4	5 (2.5)	15 (3.2)		5 (2.7)	10 (3.4)	
Clinical N stage			0.3048			0.8910
N0	32 (15.9)	85 (17.9)		32 (17.0)	58 (19.7)	
N1	158 (78.6)	346 (72.8)		145 (77.1)	214 (72.5)	
N2	8 (4.0)	35 (7.4)		8 (4.3)	18 (6.1)	
N3	3 (1.5)	9 (1.9)		3 (1.6)	5 (1.7)	
Breast Surgery type			0.2937			-
Breast Conserving Surgery	96 (47.8)	206 (43.4)		89 (47.3)	136 (46.1)	

PSM: propensity score matching, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection.

† P-value by Pearson chi-square test

‡ P-value by Conditional Logistic Regression

-: matched specifically for the breast surgery type and adjuvant radiation before PSM.

	Before PSM			After PSM		
Total Mastectomy	105 (52.2)	269 (56.6)		99 (52.7)	159 (53.9)	
Number of positive SLN(s)			< .0001			0.7212
1	144 (71.6)	235 (49.5)		132 (70.2)	195 (66.1)	
2	44 (21.9)	168 (35.4)		43 (22.9)	72 (24.4)	
3	13 (6.5)	72 (15.2)		13 (6.9)	28 (9.5)	
Adjuvant Radiation			0.0486			-
no	43 (21.4)	72 (15.2)		39 (20.7)	57 (19.3)	
yes	158 (78.6)	403 (84.8)		149 (79.3)	238 (80.7)	
Adjuvant Endocrine Therapy			0.7517			0.5886
no	36 (17.9)	90 (18.9)		30 (16.0)	43 (14.6)	
yes	165 (82.1)	385 (81.1)		158 (84.0)	252 (85.4)	
PSM: propensity score matching, SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection.						
† P-value by Pearson chi-square test						
‡ P-value by Conditional Logistic Regression						
-: matched specifically for the breast surgery type and adjuvant radiation before PSM.						

Among 483 matched patients, 188 were in the SLNB only group and 295 were in the ALND group. Age at diagnosis, tumor biology, clinical T and N stage, breast surgery type, the number of metastatic nodes during SNB, adjuvant radiation, endocrine therapy were included for matching [Table 1].

Survival outcomes

Both univariate and multivariable-adjusted analyses exhibited no significant differences in survival regardless of the recurrence sites or overall survival in unmatched cohorts (Table 2). The data were adjusted for the variables listed in Table 1. Specifically, axillary recurrence (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.36–1.70, p = 0.54), regional recurrence (HR 1.15, 95% CI 0.63–2.11, p = 0.65), distant metastasis (HR 1.16, 95% CI 0.73–1.82, p = 0.53), and death (HR 1.35, 95% CI 0.48–3.84, p = 0.56) showed no statistically significant differences between the SLNB only and ALND groups in the multivariable-adjusted analysis.

Table 2
Cox analysis results of the axillary and regional recurrence, distant metastasis, and death.

	Univariable				**Multivariable adjusted[a]**		**Propensity score matching**			
	No of events	5-year survival probability (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	No of events	5-year survival probability (%)	HR[b] (95% CI)	P-value
Axillary Recurrence										
SLNB only	11	93.6	1(Ref)		1(Ref)		11	93.1	1(Ref)	
ALND	27	92.3	0.99 (0.49-2.00)	0.973	0.79 (0.36–1.70)	0.542	17	92.3	0.94 (0.43–2.05)	0.876
Regional Recurrence										
SLNB only	15	91.6	1(Ref)		1(Ref)		15	91.0	1(Ref)	
ALND	51	82.7	1.35 (0.76–2.40)	0.310	1.15 (0.63–2.11)	0.656	26	82.8	1.00 (0.53–1.90)	0.998
Distant Metastasis										
SLNB only	26	85.7	1(Ref)		1(Ref)		26	84.7	1(Ref)	
ALND	89	65.6	1.34 (0.86–2.07)	0.196	1.16 (0.73–1.82)	0.534	50	59.1	1.07 (0.67–1.70)	0.790
Death										
SLNB only	5	97.4	1(Ref)		1(Ref)		4	97.8	1(Ref)	
ALND	21	91	1.64 (0.62–4.38)	0.321	1.35 (0.48–3.84)	0.569	12	89.3	1.65 (0.58–4.65)	0.347

SLNB: sentinel lymph node biopsy, ALND: axillary lymph node dissection HR: hazard ratio, CI: confidence interval

a. Adjusted for variables listed in Table 1

b. Cox proportional hazards model with robust standard errors to account for clustering in matched pairs

For matched cohorts, stratified log-rank test and Cox regression analyses showed no significant differences in both 5-year survival probability and hazard ratio for the various types of recurrences and for overall survival between the two groups.

After matching, we observed no statistically significant difference in axillary recurrence (HR 0.94, 95% CI 0.43–2.05, p = 0.87), regional recurrence (HR 1.0, 95% CI 0.53–1.90, p = 0.99), distant metastasis (HR 1.07, 95% CI 0.67–1.70, p = 0.79), and death (HR 1.65, 95% CI 0.58–4.65, p = 0.34) [Table 2]. Kaplan-Meier survival curve for the matched cohort showed no significant differences between SLNB and ALND groups in axillary, regional, distant metastasis-free survival, and overall survival [Fig. 1.].

We performed subgroup analysis based on breast surgery type and radiation therapy. The results for patients who underwent breast conserving surgery and demonstrated axillary recurrence were (HR 0.87, 95% CI 0.27–2.80, p = 0.82), regional recurrence (HR 1.09, 95% CI 0.40–3.02, p = 0.86), distant metastasis (HR 1.15, 95% CI 0.56–2.35, p = 0.71), and death (HR 2.33, 95% CI 0.60–9.14, p = 0.22) without significant difference between the SLNB only and ALND groups. The outcomes for patients who underwent total mastectomy and showed axillary recurrence were (HR 0.99, 95% CI 0.35–2.82, p = 0.98), regional recurrence (HR 0.93, 95% CI 0.40–2.16, p = 0.87), distant metastasis (HR 1.01, 95% CI 0.54–1.88, p = 0.98), and death (HR 1.06, 95% CI 0.19–5.93, p = 0.95) without substantial difference between the two groups [Table 3].

Table 3
Cox analysis results after propensity matching according to breast surgery type.

	PSM	
	HR[a] (95% CI)	P-value
Axillary Recurrence		
Breast Conserving Surgery	0.87 (0.27–2.80)	0.822
Mastectomy	0.99 (0.35–2.82)	0.985
Regional Recurrence		
Breast Conserving Surgery	1.09 (0.40–3.02)	0.862
Mastectomy	0.93 (0.40–2.16)	0.874
Distant Metastasis		
Breast Conserving Surgery	1.15 (0.56–2.35)	0.710
Mastectomy	1.01 (0.54–1.88)	0.981
Death		
Breast Conserving Surgery	2.33 (0.60–9.14)	0.224
Mastectomy	1.06 (0.19–5.93)	0.951

HR: hazard ratio, PSM: propensity score matching; CI confidence interval, ALND: axillary lymph node dissection, SLNB, sentinel lymph node biopsy

a. Cox proportional hazards model with robust standard errors to account for clustering in matched pairs

HR for with ALND (reference group = SLNB only)

The results for patients who did not receive radiation therapy but exhibited axillary recurrence were (HR 1.49, 95% CI 0.38–5.89, p = 0.57), regional recurrence (HR 1.20, 95% CI 0.34–4.20, p = 0.78), distant metastasis (HR 1.13, 95% CI 0.30–4.24, p = 0.85), and death (HR 1.02, 95% CI 0.68–1.53, p = 0.91) without significant difference between the SLNB only and ALND groups. The outcomes for patients who received radiation therapy and showed axillary recurrence (HR 0.75, 95% CI 0.29–1.94, p = 0.55), regional recurrence (HR 0.93, 95% CI 0.44–1.97, p = 0.85), distant metastasis (HR 1.05, 95% CI 0.64–1.74, p = 0.83), and death (HR 1.65, 95% CI 0.56–4.83, p = 0.36) were not significantly different between the two groups [Table 4].

Table 4
Cox analysis results after propensity matching according to adjuvant radiation.

	PSM	
	HR[a] (95% CI)	P-value
Axillary Recurrence		
without radiation	1.49 (0.38–5.89)	0.572
radiation	0.75 (0.29–1.94)	0.553
Regional Recurrence		
without radiation	1.20 (0.34–4.20)	0.780
radiation	0.93 (0.44–1.97)	0.856
Distant Metastasis		
without radiation	1.13 (0.30–4.24)	0.853
radiation	1.05 (0.64–1.74)	0.837
Death		
without radiation	1.02 (0.68–1.53)	0.912
radiation	1.65 (0.56–4.83)	0.361

HR: hazard ratio, PSM: propensity score matching, CI: confidence interval, ALND: axillary lymph node dissection, SLNB, sentinel lymph node biopsy

a. Cox proportional hazards model with robust standard errors to account for clustering in matched pairs

HR for with ALND (reference group = SLNB only)

Discussion

Since the publication of the ACOSOG Z0011 trial, incorporating its result into clinical practice led to replacing a significant portion of ALND to SLNB for patients with clinical T1-2 N0 primary breast cancer. [7, 8] To date, ALND has been the standard method of choice for the surgery of patients with positive nodes prior to NAC, regardless of response. Although traditional axillary surgery has its firm foundation, optimal management of the axilla continues to evolve so as to reduce its related morbidity. Nguyen et al. observed a significant shift in axillary surgery for clinical node-positive patients treated with NAC, with the increasing use of SLN, and decreasing use of ALND, to assess nodal status after preoperative treatment. [9] Also, de-escalation of axillary surgery after NAC has been increasing, but important prospective data regarding recurrence and survival are lacking. [10] Residual tumor cells in the lymph nodes following NAC may represent a selective population of chemotherapy-resistant cells, and whether or not they can be safely managed without an axillary dissection is unclear. [11] Appropriate optimal management of node-positive axilla following NAC needs further clinical evidence. We aimed to analyze recurrence-free survival and overall survival results in patients with 1–3 positive SLNs after NAC with or without complete ALND.

SLNB alone after 1–3 positive SLNs during surgery following NAC may lead to a concern of possible residual nodal disease and inferior outcome in terms of disease recurrence or overall survival. However, our investigation suggests that no statistically significant differences were observed in the axillary, regional, and distant recurrence and overall survival for matched cohorts. It is also notable that axillary recurrence was present in 11 patients in the SLNB only group (188 patients, 5.8%) and in 17 patients in the ALND group (296 patients, 5.7%), which resulted in a HR of 0.94 (0.43–2.05, p = 0.87) using the Cox proportional hazards model with robust standard errors. The axillary failure did not differ significantly based on the extent of nodal dissection. Five-year survival probability showed no significant differences between the two groups. Death occurred in 4 patients in the SLNB only group (188 patients, 2.1%) and in 12 patients in the ALND group (296 patients, 4.0%) with a 5-year survival probability of 97.7% and 97.3% (p = 0.39), respectively.

Provision of appropriate adjuvant treatment, including radiation and endocrine therapy, may be one of the possible explanations for these results. In this study, standard radiation and endocrine therapy were provided for suitable patients as part of adjuvant treatment. Regional irradiation was performed on approximately 80% of both groups of matched patients. (79.3% of SLNB alone, 80.7% of ALND). Endocrine treatment was provided for 84% of patients in the SLNB group and for 85.4% of patients in the ALND group.

As regards the question of whether axillary radiation therapy is comparable to ALND in terms of local control, the AMAROS trial concluded non-inferiority of axillary radiotherapy to ALND for T1-2 primary breast cancer and no palpable lymphadenopathy, and it expressly excluded patients with NAC.
[12] A similar question for patients with positive sentinel node(s) after completion of NAC is being assessed in the Alliance A11202 trial, the estimated primary completion date of which is January 2024 (NCT 01901094). Radiation therapy is one of the major factors influencing local control. We performed a subgroup analysis based on the matched cohorts with or without adjuvant radiation. Our data show no significant difference in outcomes of axillary, regional, and distant recurrence and death between the SLNB only group and ALND group. However, the aim of this study is not to decide on the effectiveness of radiation therapy after NAC, rather it was to identify the outcomes following comprehensive treatment modalities.

We found one preliminary analysis about a positive sentinel node on SLNB after NAC for the omission of ALND. [13] The authors suggest that the 3-year regional control rate did not differ according to the extent of axillary surgery (92.6% for SLNB alone vs. 96.4% for SLNB with ALND, p = 0.616) and resulted in lower rates of lymphedema. Our study has a longer median follow-up period and covered 1–3 positive SLNs. Our data support that axillary management may be reduced from ALND to SLNB alone when 1–3 positive SLNs are identified during surgery following NAC, without significant compromise of outcomes in terms of disease recurrence and overall survival.

This study has several limitations. Beyond the retrospective nature of our analysis, we would admit that there could be a potential selection bias in the eligible SLNB patients who might be good responders to NAC. Substantial heterogeneity of the baseline data might exist compared to that obtained in a prospective investigation. In addition, our study was based at a single institution and data were collected from eight different breast surgeons. Furthermore, the intraoperative decision threshold for ALND after 1–3 SLN metastasis and axillary surgical extent for ALND are not always uniform among surgeons. This may partially reflect the reality of current clinical practice. To minimize this limitation, we attempted to stratify each patient's baseline characteristics and performed PSM for all available patients, cancer burden, surgery type, and adjuvant treatment-related variables. Another limitation is the length of the follow-up period. The median follow-up period was 59.4 (range 7.3–153) months after surgery. We calculated the 5-year survival probabilities of the matched cohorts by stratified log-rank test and compared these between the two groups with the number of actual patients during the investigation time window. However, the outcome might need further validation over the long term.

Conclusions

Our results may add to the supporting evidence for clinical decision-making to endorse less extensive axillary surgery after limited residual axillary disease burden following NAC. Our analysis suggests that SLNB alone may be a possible option for patients with intraoperative 1–3 sentinel node-positive disease following NAC without significant compromise of outcomes in terms of recurrence or overall survival.

Declarations

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Ethicalapproval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of Interest statement

The authors declare that they have no conflict of interest.

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Figures

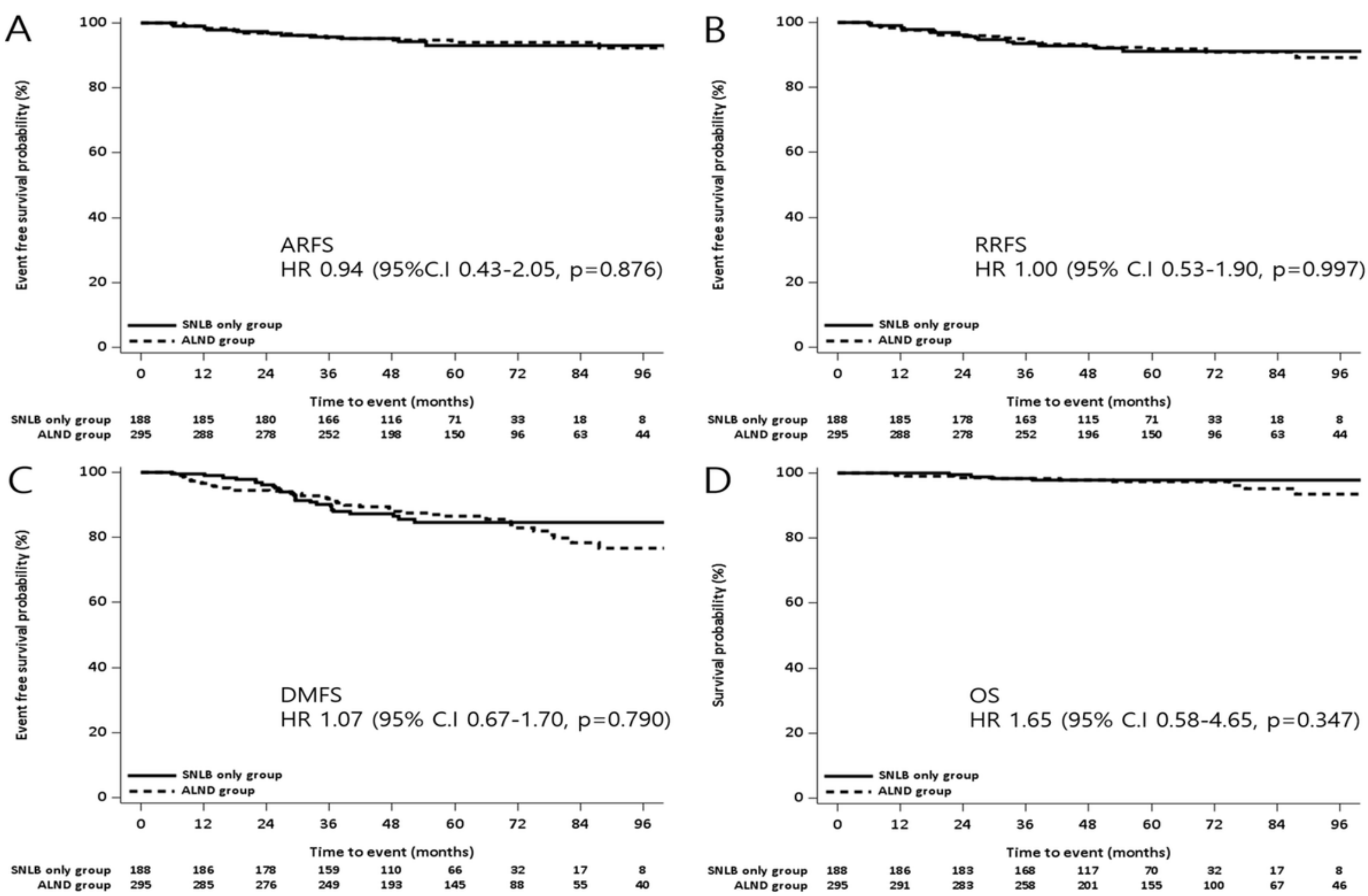

Figure 1

Survival analysis after propensity score matching (PSM) of the Axillary Recurrence-Free Survival (ARFS) (A), Regional Recurrence-Free Survival (RRFS) (B), Distant Metastasis-Free Survival (DMFS) (C), and Overall Survival (OS) (D) between the sentinel lymph node biopsy (SNLB) only and axillary lymph node dissection (ALND) groups.