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Oncologic Outcomes of Immediate Breast Reconstruction in the Setting of Neoadjuvant Chemotherapy: A Long-term Follow-up Study of a Matched Cohort

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ABSTRACT

Purpose: Despite the increasing use of immediate breast reconstruction (IBR), its oncologic safety in the setting of neoadjuvant chemotherapy (NACT) needs to be comprehensively clarified in breast cancer management. The objective of the present study was to analyze the oncologic safety of IBR following NACT.

Methods: In total, 587 patients with breast cancer who underwent a total mastectomy (TM) with IBR after NACT between 2008 and 2017 at a single institution were retrospectively reviewed. The reviewed patients with IBR following skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) were matched 1:3 to patients who underwent TM alone after NACT. Matching variables included age, clinical T and N stages before NACT, response to NACT, pathologic T and N stages, and molecular subtypes.

Results: After propensity score matching, 95 patients who underwent IBR following SSM/NSM after NACT (IBR group) and 228 patients who underwent TM alone after NACT (TM group) were selected. The median follow-up period was 73 (range, 5–181) months after matching. After matching, there were no significant differences between the two groups in 5-year locoregional recurrence-free survival (88.8% vs. 91.2%, $p = 0.516$), disease-free survival (67.3% vs. 76.6%, $p = 0.099$), distant metastasis-free survival (71.9% vs. 81.9%, $p = 0.057$), or overall survival (84.1% vs. 91.5%, $p = 0.061$) rates. In multivariate analyses, conducting IBR was not associated with increased risks for locoregional recurrence, any recurrence, distant metastasis, or overall death.

Conclusion: Our findings suggest that IBR following SSM/NSM elicits comparable long-term oncologic outcomes to those of TM alone in the setting of NACT.

Keywords: Breast Neoplasms; Mammoplasty; Mastectomy, Simple; Neoadjuvant Therapy

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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: Shin DS, Bang YJ, Lee KT, Ryu JM; Data curation: Bang YJ, Chae BJ, Yu J, Lee JE, Kim SW, Nam SJ, Jeon BJ, Pyon JK, Mun GH; Formal analysis: Shin DS; Funding acquisition: Ryu JM; Investigation: Bang YJ, Jang SY, Kwak Y; Methodology: Choi JY, Lee H; Supervision: Ryu JM; Visualization: Shin DS; Writing - original draft: Shin DS; Writing - review & editing: Shin DS, Lee KT, Ryu JM.

INTRODUCTION

Neoadjuvant chemotherapy (NACT) can reduce the surgical burden by rendering the previously inoperable disease operable, enabling breast-conserving surgery (BCS) in patients who would otherwise require a total mastectomy (TM), and reducing the rate of axillary lymph node dissection. However, even after NACT, TM may need to be considered owing to extensive previous tumor size, further disease progression, and patient preference [1-4].

Female patients who underwent TM were more likely to experience anxiety and depression, which negatively impacted their self-perceived sexual attractiveness and self-esteem, and they were more dissatisfied with the cosmetic results of their surgery than females who underwent BCS or concurrent reconstruction surgery [5-7]. Immediate breast reconstruction (IBR) is a growing surgical option to overcome these negative aspects of TM and has been found to afford comparable oncologic safety to TM alone [8-10].

IBR may also be a good surgical option in patients receiving NACT [11]. Recent studies have reported that IBR after NACT is feasible and non-inferior to TM for oncologic stability in certain investigations. Unfortunately, no prospective studies have been reported, and there are few long-term follow-up results [12,13].

The current study was an extension of the short-term study previously conducted at our institution and was designed to analyze the oncologic outcomes of patients who had TM alone or IBR following skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) after NACT with more than a median 6-year follow-up.

METHODS

Data collection

Clinical data of patients with breast cancer who had undergone mastectomy following NACT between January 2008 and December 2017 at Samsung Medical Center in Seoul, South Korea, were collected retrospectively. We excluded patients with progressive disease status during or after NACT and with synchronous distant metastasis (DM) at the time of diagnosis. Selected patients were divided into two groups: TM-alone (control group) and IBR following SSM or NSM (study group). The two groups were matched by 1:3 propensity scores, where matching variables included age, clinical T and N stages before NACT, response to NACT, pathologic T and N stages after NACT, and estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor 2 (HER2) status. Pathologic and clinical staging in this study was determined according to the 8th edition of the American Joint Committee on Cancer classification.

Locoregional recurrence (LRR) was defined to include breast cancer recurrence in the ipsilateral chest wall, skin, subcutaneous tissue, or pectoralis muscle as a local recurrence or within the ipsilateral axillary, supraclavicular, internal mammary, or infraclavicular lymph nodes as a regional recurrence. DM was defined as any recurrence in locations outside of those covered by LRR. Information on recurrence events was acquired by reviewing electronic medical records, and survival data were collected from the electronic medical records and the Korean National Statistical Office database. All patients in the current study received NACT according to the directions of the oncologist, who also decided on the

treatment with trastuzumab concurrently or as an adjuvant regimen. Mastectomy, including SSM or NSM, was performed by a breast surgeon, and IBR was conducted by a plastic surgeon after the mastectomy. The type of IBR was selected at the preoperative consultation with the plastic surgeon according to the patient's preferences and disease presentation. In all cases with NSM, the margin of resection under the nipple was confirmed to be negative for malignant cells on the frozen section intraoperatively.

The need for informed consent was waived because the study was conducted retrospectively. The approval for the current study, which complied with the ethical tenets of the Declaration of Helsinki, was granted by the Institutional Review Board (IRB) of Samsung Medical Center in Seoul, Korea (IRB number: 2021-06-126).

Statistical analysis

Weighted independent t-tests for continuous variables and weighted χ^2 or Fisher's exact tests for categorical variables were used to compare patient characteristics. With the corresponding results of log-rank tests, Kaplan-Meier curves were conducted for locoregional recurrence-free survival (LRFS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and overall survival (OS). The primary endpoint of this study was LRFS. Each recurrence was counted as a separate event in cases of simultaneous LRR or DM. The follow-up duration was calculated from the date of surgery.

We used the propensity score matching method to reduce bias between the two groups for certain characteristics that impact prognosis. The matching was conducted using the nearest neighbor matching method with a caliper of 0.2 for all patients. To extract the 1:3 propensity score matching dataset, 7 variables, including age, clinical T and N stages before NACT, response to NACT, pathologic T and N stages, and molecular subtypes associated with the outcomes, were applied. We used the standardized mean difference (SMD) to assess balance after propensity score matching. We considered balance to be achieved when the absolute value of SMD was less than 0.1.

The univariate and multivariate Cox proportional hazards regression models were used to examine the clinicopathological variables related to LRFS, DFS, DMFS, and OS for the matched groups. All statistical analyses were executed using SAS version 9.4 (SAS Institute, Cary, USA) and R version 4.0.2 (Vienna, Austria; <http://www.R-project.org/>). Two-sided *p*-values < 0.05 were considered statistically significant.

RESULTS

Study design

The schematic diagram for the present study is shown in **Figure 1**. Among 631 patients with TM after NACT, we excluded 44 patients with progression during NACT. After propensity score matching by age, the clinical stage before NACT, response to NACT, pathologic stage after NACT, and ER/PR/HER2 status, 228 patients were included in the TM-alone group and 95 patients in the IBR group. The matching for all 7 variables was successful and balanced, indicating that the absolute value of the SMD for each variable was less than 0.1 (**Figure 2**).

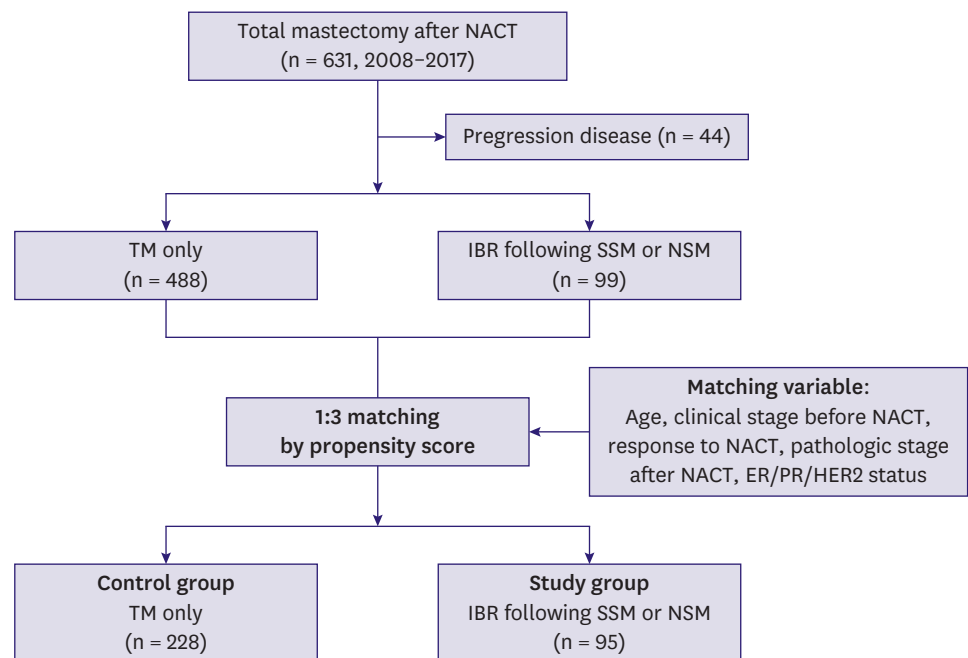


Figure 1. Schematic diagram of patient selection for matched study.

NACT = neoadjuvant chemotherapy; TM = total mastectomy; IBR = immediate breast reconstruction; SSM = skin-sparing mastectomy; NSM = nipple-sparing mastectomy; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

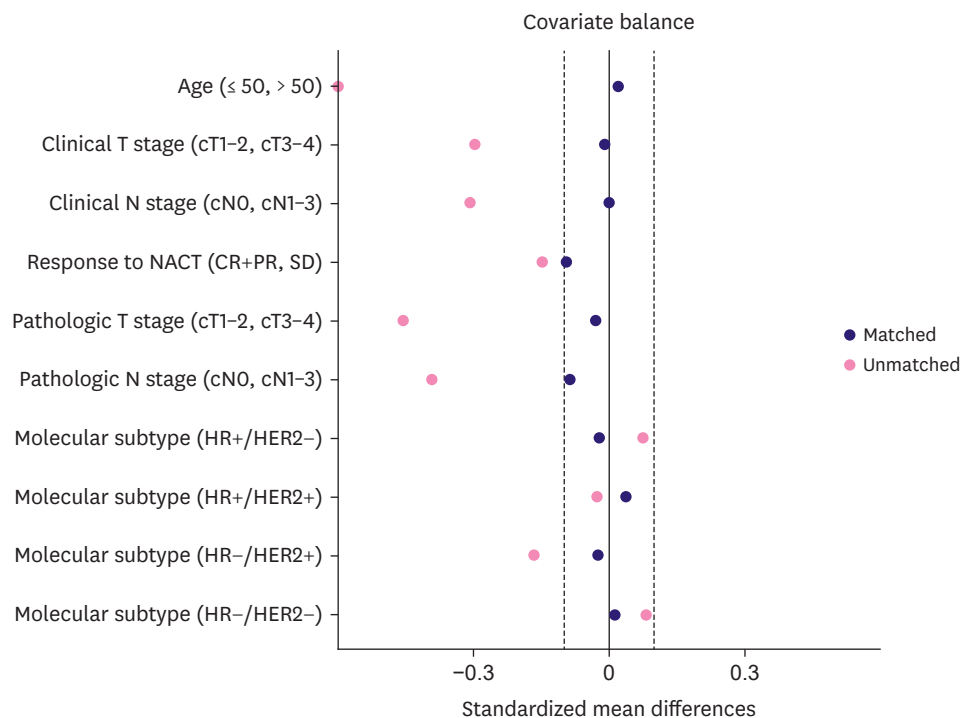


Figure 2. Love plot for covariate balance between matched and unmatched groups.

NACT = neoadjuvant chemotherapy; CR = complete response; PR = partial response; SD = stable disease; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

Patient characteristics

Table 1 summarizes the baseline clinicopathologic characteristics of the control and study groups before matching. The mean age for the control and study groups were 46.5 ± 8.9 and 38.6 ± 6.6 years, respectively ($p < 0.001$). Patients under 50 years comprised 67.2% and 94.9% of the control and study groups, respectively, before matching ($p < 0.001$). The two groups differed significantly in clinical T and N stages before NACT, nuclear grade, histologic grade, pathologic T and N stage after NACT, and response to NACT before matching, but not in body mass index (BMI) or subtypes of cancer. The clinicopathologic characteristics of the two groups after 1:3 matching are shown in **Table 2**. After matching, the median follow-up durations were 74.5 (range, 5–181) months for the control group and 73.0 (range, 6–153) months for the study group. The mean age of the patients at diagnosis was 42.7 ± 6.9 years in the control group and 38.8 ± 6.7 years in the study group ($p < 0.001$). There were no statistically significant differences in the proportion of patients aged 50 years or younger in each group (94.3% in the control group vs. 94.7% in the study group; $p = 0.594$). There were no significant differences between the two groups with respect to BMI, hormone receptor (HR) status, HER2 status, clinical T and N stage before NACT, histologic grade, pathologic T

Table 1. Baseline characteristics of patients who underwent immediate breast reconstruction and skin-sparing mastectomy/nipple-sparing mastectomy (study group) or total mastectomy alone (control group) before matching

Variables	Control group (n = 488)	Study group (n = 99)	p-value
Age (yr)	46.5 ± 8.9	38.6 ± 6.6	< 0.001
≤ 50	328 (67.2)	94 (94.9)	< 0.001
> 50	160 (32.8)	5 (5.1)	
BMI (kg/m ²)	24.0 ± 3.5	23.3 ± 3.6	0.034
≤ 25	333 (68.2)	77 (77.8)	0.059
> 25	155 (31.8)	22 (22.2)	
Clinical T stage			0.006
cT1-2	175 (35.9)	50 (50.5)	
cT3-4	313 (64.1)	49 (49.5)	
Clinical N stage			0.002
cN0	13 (2.7)	10 (10.1)	
cN1	111 (22.8)	31 (31.3)	
cN2	219 (44.9)	42 (42.4)	
cN3	145 (29.7)	16 (16.2)	
Molecular subtype			0.484
HR+/HER2–	199 (40.8)	44 (44.4)	
HR+/HER2+	84 (17.2)	16 (16.2)	
HR–/HER2+	94 (19.3)	13 (13.1)	
HR–/HER2–	111 (22.8)	26 (26.3)	
Histologic grade			0.003
Grade 1	65 (13.3)	15 (15.2)	
Grade 2	205 (42.0)	44 (44.4)	
Grade 3	189 (38.7)	25 (25.3)	
Unknown	29 (5.9)	15 (15.2)	
Pathologic T stage			< 0.001
ypT0-1	192 (39.3)	61 (61.6)	
ypT2-3	296 (60.7)	38 (38.4)	
Pathologic N stage			< 0.001
ypN0	192 (39.3)	58 (58.6)	
ypN1-3	296 (60.7)	41 (41.4)	
Response to NACT			0.013
CR	26 (5.3)	13 (13.1)	
PR	306 (62.7)	61 (61.6)	
No response	156 (32.0)	25 (25.3)	

Data are shown as mean ± standard deviation or number (%).

BMI = body mass index; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; NACT = neoadjuvant chemotherapy; CR = complete response; PR = partial response.

Table 2. Characteristics of patients who underwent immediate breast reconstruction after skin-sparing mastectomy/nipple-sparing mastectomy (study group) or total mastectomy alone (control group) after matching

Variables	Control group (n = 228)	Study group (n = 95)	p-value
Age (yr)	42.7 ± 6.9	38.8 ± 6.7	< 0.001
≤ 50	215 (94.3)	90 (94.7)	0.594
> 50	13 (5.7)	5 (5.3)	
BMI (kg/m ²)	23.6 ± 3.3	23.4 ± 3.6	0.993
≤ 25	164 (71.9)	74 (77.9)	0.407
> 25	64 (28.1)	21 (22.1)	
Clinical T stage			0.852
cT1-2	100 (43.9)	48 (50.5)	
cT3-4	128 (56.1)	47 (49.5)	
Clinical N stage			> 0.999
cN0	9 (4.0)	6 (6.3)	
cN1	54 (23.7)	31 (32.6)	
cN2	107 (46.9)	42 (44.2)	
cN3	58 (25.4)	16 (16.8)	
Molecular subtype			0.887
HR+/HER2-	101 (44.3)	43 (45.3)	
HR+/HER2+	39 (17.1)	16 (16.8)	
HR-/HER2+	39 (17.1)	13 (13.7)	
HR-/HER2-	49 (21.5)	23 (24.2)	
Histologic grade			0.210
Grade 1	37 (16.2)	15 (15.8)	
Grade 2	89 (39.0)	44 (46.3)	
Grade 3	87 (38.2)	24 (25.3)	
Unknown	15 (6.6)	12 (12.6)	
Pathologic T stage			0.605
ypT0-1	117 (51.3)	57 (60.0)	
ypT2-3	111 (48.7)	38 (40.0)	
Pathologic N stage			0.131
ypN0	100 (43.9)	54 (56.8)	
ypN1-3	128 (56.1)	41 (43.2)	
Response to NACT			0.152
CR	11 (4.8)	10 (10.5)	
PR	137 (60.1)	60 (63.2)	
No response	80 (35.1)	25 (26.3)	

Data are shown as mean ± standard deviation or number (%).

BMI = body mass index; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; NACT = neoadjuvant chemotherapy; CR = complete response; PR = partial response.

and N stage after NACT, or response to NACT after the propensity score matching. Given that patients with progressive disease during NACT did not undergo IBR, they were excluded from this study. In the control group, 11 patients (4.8%) had a complete response, 137 patients (60.1%) had a partial response, and 80 patients (35.1%) had stable disease after NACT. In the study group, 10 patients (10.5%) had a complete response, 60 patients (63.2%) had a partial response, and 25 patients (26.3%) had stable disease after NACT.

Type of surgical and adjuvant treatments

In the current study, all patients underwent NACT after a diagnosis of invasive breast cancer followed by mastectomy. In the study group, 31 patients (32.7%) underwent NSM, and 64 patients (67.3%) underwent SSM. Among the 95 patients who underwent IBR after SSM/NSM, 60 patients (63.2%) underwent tissue expander insertion, 33 patients (34.7%) underwent deep inferior epigastric perforator flap, and 2 patients (2.1%) underwent latissimus dorsi flap. A higher number of patients in the control group underwent axillary lymph node dissection than those in the study group (83.3% vs. 52.6%, $p < 0.001$). The two groups did not differ significantly in terms of adjuvant hormonal therapy or trastuzumab for

Table 3. Characteristics of surgical and medical treatment after matching

Variables	Control group (n = 228)	Study group (n = 95)	p-value
Type of TM			NA
NSM	0 (0)	31 (32.7)	
SSM	0 (0)	64 (67.3)	
Conventional TM	228 (100)	0 (0)	
Axillary surgery			< 0.001
SLNB only	38 (16.7)	45 (47.4)	
ALND	190 (83.3)	50 (52.6)	
Type of IBR			NA
TEI	0 (0)	60 (63.2)	
DIEP	0 (0)	33 (34.7)	
LD flap	0 (0)	2 (2.1)	
NACT regimen			0.005
AC+T	163 (71.5)	81 (85.3)	
Others	65 (28.5)	14 (14.7)	
Adjuvant radiotherapy			0.011
Yes	197 (86.4)	71 (74.7)	
No	31 (13.6)	24 (25.3)	
Adjuvant hormonal therapy			0.594
Yes	139 (61.0)	62 (65.3)	
No	88 (38.6)	32 (33.7)	
Unknown	1 (0.4)	1 (1.1)	

Values are presented as number (%).

TM = total mastectomy; NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy; NA = not applicable; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; IBR= immediate breast reconstruction; TEI = tissue expander insertion; DIEP = deep inferior epigastric perforator flap; LD = latissimus dorsi; NACT = neoadjuvant chemotherapy; AC+T = anthracycline and cyclophosphamide followed by taxane.

HER2-positive patients ($p = 0.594$ or $p = 0.544$, respectively). The control group had a higher number of patients who received post-mastectomy radiation therapy (PMRT) than the study group (86.4% vs. 74.7%, $p = 0.011$) (**Table 3**).

Oncologic outcomes

The TM-alone and IBR after SSM/NSM groups did not differ significantly in terms of local recurrence-free survival and regional recurrence-free survival (weighted log-rank test, $p = 0.776$ and $p = 0.829$, respectively). As shown in **Table 4**, of the 228 patients who underwent conventional TM alone (control group), 14 (6.1%) had local recurrence, 16 (7.0%) experienced regional recurrence, and 80 (35.1%) had DM. Of the 95 patients who underwent IBR (study group), 4 (4.2%) had local recurrence, 5 (5.3%) had regional recurrence, and 19 (20.0%) had DM. Overall, 92 patients (40.4%) in the control group and 25 (26.3%) in the study group had experienced cancer recurrence, and 57 patients (25.0%) in the control group and 10 patients (10.5%) in the study group died during the follow-up period.

For both groups, Kaplan-Meier survival curves for LRFS (weighted log-rank test, $p = 0.725$), DFS (weighted log-rank test, $p = 0.157$), DMFS (weighted log-rank test, $p = 0.078$), and OS (weighted log-rank test, $p = 0.060$) are shown in **Figure 3**. The control and study groups did not differ significantly in terms of LRFS, DFS, DMFS, and OS rates. The control and study groups exhibited 5-year LRFS rates of 88.8% (95% confidence interval [CI], 83.0–92.7) and 91.2% (95% CI, 83.2–95.5), respectively ($p = 0.516$), whereas the 5-year DFS rates were 67.3%

Table 4. Analysis of oncologic outcomes in the two groups after matching

Patient group	Total	Local recurrence	Regional recurrence	Any recurrence	Distant recurrence	Death
Control group	228 (70.6)	14 (6.1)	16 (7.0)	92 (40.4)	80 (35.1)	57 (25.0)
Study group	95 (29.4)	4 (4.2)	5 (5.3)	25 (26.3)	19 (20.0)	10 (10.5)

Values are presented as number (%).

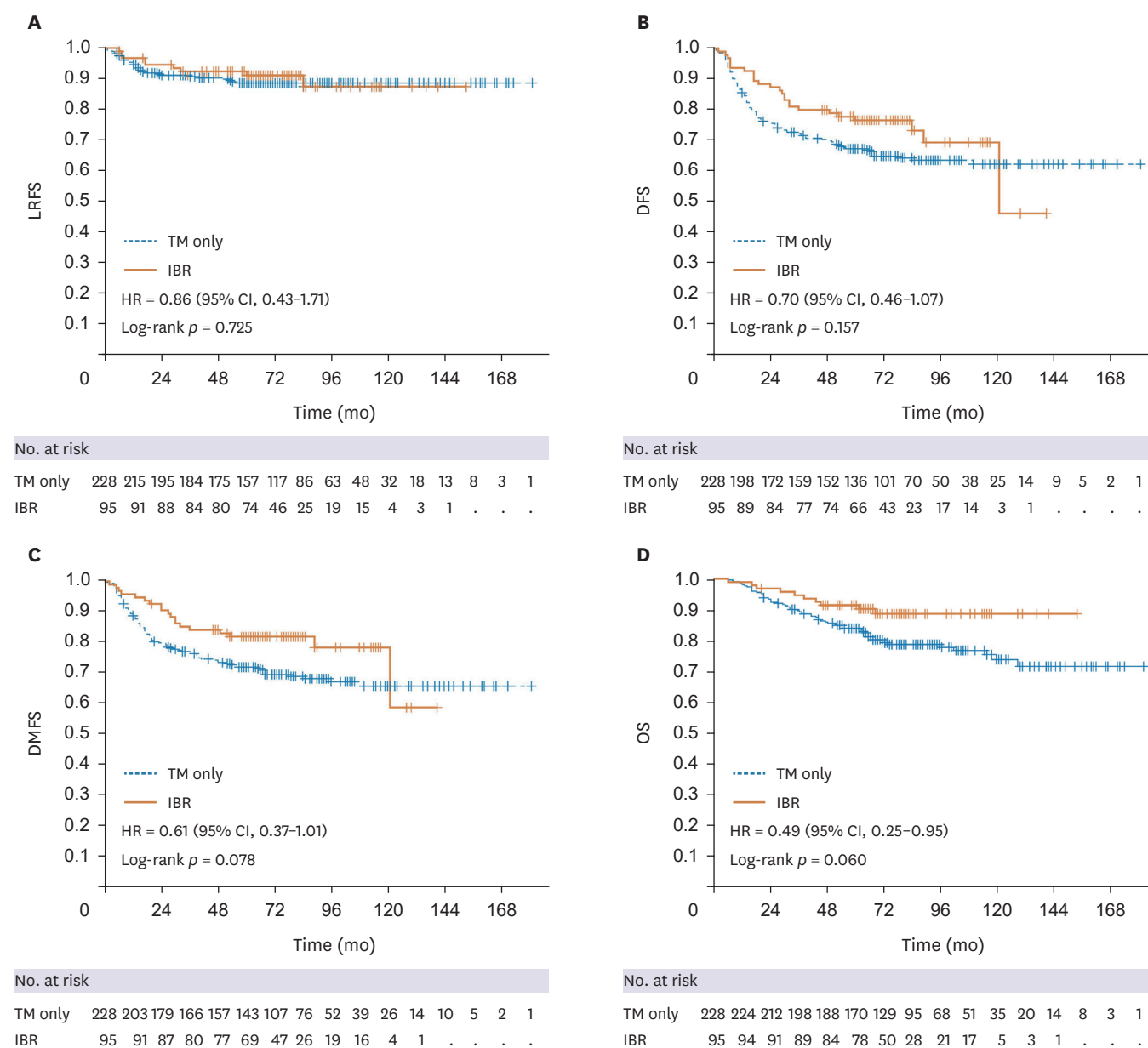


Figure 3. Kaplan-Meier curves for the two matched group.

(A) LRFS. (B) DFS. (C) DMFS. (D) OS.

LRFS = locoregional recurrence-free survival; TM = total mastectomy; IBR = immediate breast reconstruction; HR = hormone receptor; CI = confidence interval; DFS = disease-free survival; DMFS = distant metastasis-free survival; OS = overall survival.

(95% CI, 59.8-73.7) and 76.6% (95% CI, 66.7-83.9) ($p = 0.099$), respectively. The 5-year DMFS and OS rates were 71.9% (95% CI, 64.6-78.0) and 84.1% (95% CI, 77.8-88.7) in the control group and 81.9% (95% CI, 72.5-88.3) and 91.5% (95% CI, 83.8-95.7) in the study group, respectively ($p = 0.057$ for 5-year DMFS rates, $p = 0.061$ for 5-year OS rates).

According to multivariate analyses with adjustment for variables, including age, clinical T and N stages before NACT, response to NACT, pathologic T and N stages, molecular subtypes, and radiotherapy, IBR was not associated with increased risks for LRR (adjusted HR, 0.85; 95%

Table 5. Univariable and multivariable analyses of factors associated with locoregional recurrence after matching

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Immediate reconstruction				
Control group (TM only)	Ref		Ref	
Study group (IBR)	0.856 (0.430–1.707)	0.659	0.845 (0.408–1.749)	0.650
Age (yr)				
≤ 50	Ref		Ref	
> 50	1.180 (0.180–7.747)	0.863	0.916 (0.098–8.562)	0.939
Clinical T stage				
cT1-2	Ref		Ref	
cT3-4	1.615 (0.833–3.129)	0.156	1.564 (0.818–2.989)	0.176
Clinical N stage				
cN0	Ref		Ref	
cN1-3	2.927 (0.400–21.401)	0.290	2.185 (0.297–16.086)	0.443
Response to NACT				
CR+PR	Ref		Ref	
No response	1.288 (0.646–2.568)	0.472	0.916 (0.310–2.709)	0.874
Pathologic T stage				
ypT0-1	Ref		Ref	
ypT2-3	1.433 (0.754–2.724)	0.272	1.081 (0.390–2.994)	0.881
Pathologic N stage				
ypN0	Ref		Ref	
ypN1-3	3.985 (1.983–8.008)	< 0.001	6.270 (2.188–17.965)	< 0.001
Radiotherapy				
No	Ref		Ref	
Yes	1.242 (0.510–3.026)	0.633	0.452 (0.107–1.918)	0.282
Molecular subtype		0.699		0.160
HR+/HER2–	Ref		Ref	
HR+/HER2+	1.394 (0.518–3.753)	1.000	2.462 (0.757–8.008)	0.205
HR–/HER2+	1.091 (0.289–4.118)	1.000	1.496 (0.360–6.210)	1.000
HR–/HER2–	1.625 (0.577–4.577)	0.789	2.569 (0.841–7.841)	0.131

CI = confidence interval; Ref = reference; TM = total mastectomy; IBR = immediate breast reconstruction; NACT = neoadjuvant chemotherapy; CR = complete response; PR = partial response; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

CI, 0.41–1.75; $p = 0.650$), any recurrence (adjusted HR, 0.67; 95% CI, 0.43–1.06; $p = 0.089$), DM (adjusted HR, 0.64; 95% CI, 0.37–1.11; $p = 0.110$), or death (adjusted HR, 0.54; 95% CI, 0.27–1.08; $p = 0.082$) (**Table 5**).

Complications

In the current study, a total of 5 major complications with Clavien-Dindo classification III or higher were reported in the two matched groups. In the control group, one patient (0.4%) underwent reoperation owing to postoperative bleeding and hematoma. In the study group, skin necrosis requiring wound revision and debridement was identified in 4 patients (4.2%).

DISCUSSION

In the present study, patients who underwent IBR after SSM/NSM were compared with those who underwent TM alone after NACT by performing 1:3 propensity score matching with long-term follow-up of a median of 73 months. We found no significant difference in 5-year LRFS, DFS, DMFS, and OS rates between the two matched groups. On multivariate analysis, our findings revealed that IBR after SSM/NSM after NACT does not worsen breast cancer outcomes when compared with those of TM alone.

NACT is valuable in the de-escalation of breast and axillary surgery. Response to NACT, especially pathologic complete response (pCR), was associated with improved survival. With advances in chemotherapy, triple-negative breast cancer (TNBC) and HER2-positive breast cancer showed high pCR rates in the setting of NACT. Consequently, the indication of NACT in TNBC or HER2-positive breast cancer has been widened to early breast cancer and the clinical N1 stage breast cancer with a high pCR rate [14-18]. Typically, IBR is considered after NACT for patients who are young and who respond well to systemic therapy. In instances where mastectomy is essential for breast cancer therapy, IBR has been found to minimize psychological morbidity and increase the quality of life, as well as patient satisfaction following the mastectomy [19]. As the surgical option of IBR has become popular and feasible in numerous patients, the rate of BCS has decreased gradually, while that of IBR post-TM has increased [8,10,20-22]. A similar trend has been observed in patients who received NACT and in those with advanced breast cancer [23].

To date, no large-scale prospective or randomized study has explored whether SSM/NSM combined with IBR after NACT is safe in terms of the oncological aspect. According to several retrospective studies, cancer recurrence rates do not differ between the IBR with SSM/NSM and the TM-alone groups after NACT. Nonetheless, surgeons remain concerned regarding the possibility of complications that can cause delays in adjuvant treatments such as radiation or target therapy. According to a review article by Arnaout et al., patients who underwent IBR following NACT experienced an increased number of postoperative complications, delaying adjuvant radiotherapy [11]. In patients with ER-negative breast cancer, Aurilio et al. have found that IBR following SSM/NSM after NACT was associated with a considerably higher probability of local recurrence than TM alone; however, the study was not matched or balanced between groups [24].

In contrast, several studies have reported that IBR following NSM is not contraindicated after NACT and is not an independent factor in local recurrence [25,26]. In a recent systematic review and meta-analysis with a total of 17 studies comprising 3,249 patients, Varghese et al. have reported that IBR after NACT is a safe procedure and does not delay adjuvant treatment because of postoperative complications [27]. Our findings are consistent with those reported by Wu et al. A single-center study performed a 1:1 propensity score matching comparison of patients who underwent IBR with those who underwent TM alone after NACT, revealing that the oncologic outcome of the IBR group did not differ from that of the TM-alone group [13].

NSM may be considered in patients with locally advanced cancer if the resected nipple margin is pathologically tumor-free, and the range of indications for NSM is gradually expanding, especially in cases of successful stage reduction after NACT [28,29]. However, there is still insufficient evidence to demonstrate the oncologic safety of nipple- and areolar complex-sparing surgery after NACT with long-term follow-up. In this current study, we identified 9 local recurrences in 95 patients who underwent IBR with SSM or NSM after NACT. Additionally, 4 local recurrences were observed among the 31 patients who underwent NSM and 5 local recurrences among the 64 patients who underwent SSM, and the difference in local recurrences between the two groups was not statistically significant ($p = 0.427$). Results from well-controlled, large-scale, and long-term follow-up studies are needed to confirm and clarify the safety of NSM in patients who received NACT.

We performed a median 73.0-month follow-up (range, 5–181) study with more patients than those included in our previous study. Patients who underwent TM only after NACT exhibited

various clinicopathologic characteristics. Patients who underwent TM alone often presented with more advanced disease than those considered for IBR, frequently experiencing an unfavorable post-NACT response. Therefore, a comparison by propensity score matching is essential, rather than a simple comparison of two groups. Herein, we performed propensity score matching to minimize bias between two groups for selected variables that affect prognosis.

Nevertheless, our current study has some limitations. First, despite matching the important clinical factors, selection bias may persist owing to the retrospective nature of the study. Although the *p*-values exceeded 0.05 in the current study, the TM-alone group had a tendency toward worse DMFS and OS rates. Selection bias may have impacted this result, given that several patients who were supposed to undergo mastectomy would not have selected reconstruction if poor survival outcomes were expected. Moreover, patients in the TM-alone group were more likely to undergo axillary dissection and PMRT than those in the IBR group; however, there were no statistically significant differences in clinical and pathologic N stages between the matched groups. Although prospective studies are needed to identify independent variables, it is difficult to conduct randomized prospective studies in immediate reconstruction, especially because patient preference is a crucial factor when deciding on a surgical approach.

In addition, the current study included a relatively limited number of patients who underwent IBR after NACT from a single institution. The number of patients in this study was markedly small to clarify the oncologic safety of IBR following NACT. Studies from more institutions with a larger patient sample are needed to yield conclusions with robust evidence.

It is well established that the younger a patient is when diagnosed with breast cancer, the more likely they are to have a poor prognosis [30,31]. In the current study, the IBR group had a lower mean age and a higher proportion of patients aged 35 years or younger (15.8% in the TM-alone group vs. 31.6% in the IBR group; *p* = 0.003). However, the survival rates of the IBR group were not worse than those of the TM-alone group. Therefore, we can carefully consider post-mastectomy breast reconstruction following NACT as a safe surgical option even in young patients.

In conclusion, the present study found that IBR after SSM/NSM did not elicit worse long-term oncologic outcomes than TM alone in the NACT setting. Accordingly, IBR after SSM/NSM can be performed with oncological safety, compared with TM alone, in patients who underwent NACT.

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