

## ORIGINAL ARTICLE

# Oncologic Safety of Immediate Breast Reconstruction for Invasive Breast Cancer Patients: A Matched Case Control Study

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**Purpose:** The purpose of this study was to compare locoregional recurrence-free survival (LRFS) and disease-free survival (DFS) between patients undergoing mastectomy and immediate breast reconstruction (IBR) and those undergoing mastectomy alone.

**Methods:** A retrospective review of patients who underwent mastectomy and immediate breast reconstruction for resectable invasive breast cancer between 2002 and 2010 at a single center was conducted. These cases were matched to patients who underwent mastectomy alone in the same time period, performed by 1:2 matching. Matching control variables included age, tumor size, axillary lymph node metastasis, and estrogen receptor status. Overall, 189 patients were identified in the IBR group, and 362 patients were matched to this group. **Results:** In the IBR group, 75 patients (39.7%) underwent conventional total mastectomy, 78 (41.3%) underwent skin-sparing mastectomy (SSM), and 36 (19.0%) underwent nipple-sparing mastectomy (NSM). The IBR group was significantly younger than the control group

(41.9 and 45.1 years, respectively) ( $p=0.032$ ), in spite of matching between three age groups. The DFS rates were similar between the IBR group and mastectomy alone group, at 92.0% and 89.9%, respectively, at 5-year follow-up (log-rank test,  $p=0.496$ ). The 5-year LRFS was 96.2% in the IBR group and 96.4% in the mastectomy alone group (log-rank test,  $p=0.704$ ), similar to data from previous reports. Subgroup analyses for SSM or NSM patients showed no differences in LRFS and DFS between the two groups. Additionally, in stage III patients, IBR did not cause an increase in recurrence. **Conclusion:** IBR after mastectomy, including both SSM and NSM, had no negative impact on recurrence or patient survival, even in patients with advanced disease.

**Key Words:** Locoregional neoplasm recurrence, Mammoplasty, Mastectomy, Matched case-control study

## INTRODUCTION

Immediate breast reconstruction (IBR) has become a common and widely used procedure for patients with breast cancer [1]. Owing to its excellent esthetic outcomes, IBR has gained popularity and is used in an increasing proportion of patients [2,3]. This changing trend has also been demonstrated in Korea, where there has been an almost 3-fold increase in breast reconstruction cases over the last 10 years [4]. Moreover,

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beginning in April 2015, IBR is now reimbursed by the insurance system for breast cancer patients in Korea, which is expected to result in greater availability and demand in the clinic.

To obtain better cosmetic results, skin-preserving surgical techniques, such as skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM), are preferred for breast surgery when IBR is performed. However, these procedures may compromise the completeness of mastectomy, and concerns have been raised about their oncologic safety. Due to these concerns, numerous groups have reported long-term follow-up results, demonstrating comparable or even better survival in patients who underwent immediate breast reconstruction compared to those who underwent conventional mastectomy alone [1-3,5-7]. However, many of these reports lack an appropriate matched case-control group and compare survival rates with those reported in previous studies. Additionally, many of the survival rate reports are from cohorts that included patients with *in situ* cancer, resulting in a relatively high

survival rate [5,6,8,9].

In this study, we examined the oncologic safety of IBR in patients with invasive breast cancer, by comparing the survival outcomes of patients who underwent mastectomy and IBR (IBR group) with those of a matched control group who underwent mastectomy alone (mastectomy alone group).

## METHODS

This study was approved by the Institutional Review Board in Seoul National University Hospital (IRB number: 1507-097-689). Informed consent was obtained from the participants for inclusion in the study. All breast cancer patients who underwent mastectomy and IBR (IBR group) between 2002 and 2010 at Seoul National University Hospital (SNUH), Republic of Korea, were retrospectively reviewed. Only patients with newly diagnosed resectable invasive breast cancer were included. Patients with *in situ* carcinoma or metastatic breast cancer were excluded. Additionally, patients with a history of breast cancer or risk-reducing prophylactic mastectomy were also excluded.

Each case from the IBR group was matched to two control cases based on matching variables. The matched control cases from the mastectomy alone group were patients with invasive breast cancer who underwent conventional mastectomy without immediate reconstruction or with delayed reconstruction at SNUH between 2002 and 2010. Matching control variables included age (<35 years,  $\geq 35$  and <50 years, and  $\geq 50$  years), tumor size ( $\leq 2$  cm, >2 and  $\leq 5$  cm, and >5 cm), axillary lymph node metastasis (negative or positive), estrogen receptor (ER) status (<10% [negative] or  $\geq 10\%$  [positive]), and type of primary treatment (surgery or neoadjuvant chemotherapy). For patients who underwent neoadjuvant chemotherapy, clinical tumor size and axillary lymph node status were used for matching.

Clinicopathological data were obtained from SNUH Breast Cancer Center database, which is a prospectively maintained web-based database [10]. Recurrence event data were collected via review of the SNUH electronic medical records, and survival data were acquired from the Korean National Statistical Office database.

SSM involves resection of the whole breast parenchyma along with the nipple-areola complex (NAC). Resection of the skin above the tumor was performed, with only the healthy breast skin envelope being left behind. NSM is a modification of SSM that has the benefits of SSM along with preservation of the nipple-areolar skin. NSM was performed when no evidence of NAC involvement was found clinically or on breast imaging studies, including breast MRI. To confirm the lack of

cancer in the preserved nipple-areolar skin, breast tissue shaving under the nipple was performed for intraoperative frozen biopsy to confirm that there was no tumor involvement or atypical cells. The degree of skin removal in the IBR group was comparable or smaller compared to that in the mastectomy alone group.

Mastectomies were performed by a team of general surgeons and followed by immediate reconstruction by a team of plastic surgeons. Reconstructive procedures were performed with transverse rectus abdominis flaps, tissue expander insertion, implant insertion, or latissimus dorsi flaps.

Local recurrence was defined as tumor spread found within the ipsilateral anterior chest wall (skin, subcutaneous tissue, and muscle). Regional recurrence was defined as a relapse in the ipsilateral axillary, internal mammary, supraclavicular, or infraclavicular lymph nodes. Distant metastasis was defined as recurrence in all other areas. Locoregional recurrence-free survival (LRFS) was determined as the time from the date of mastectomy to the date of findings of radiologic or biopsy-proven locoregional recurrence. Disease-free survival (DFS) was determined as the time from the date of mastectomy to the date of any incidence of local, regional, or distant recurrence. Patients without any events were censored at the date of their last out-patient clinic visit. Overall survival (OS) was determined from the date of mastectomy to the date of death or last out-patient clinic visit.

The chi-square test and t-test were used to compare clinicopathological variables between the study groups and matched controls. The Kaplan-Meier survival model and the log-rank test were used to calculate LRFS, DFS, and OS. For all analyses, a  $p$ -value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics/PC software package version 22 (IBM Corp., Armonk, USA).

## RESULTS

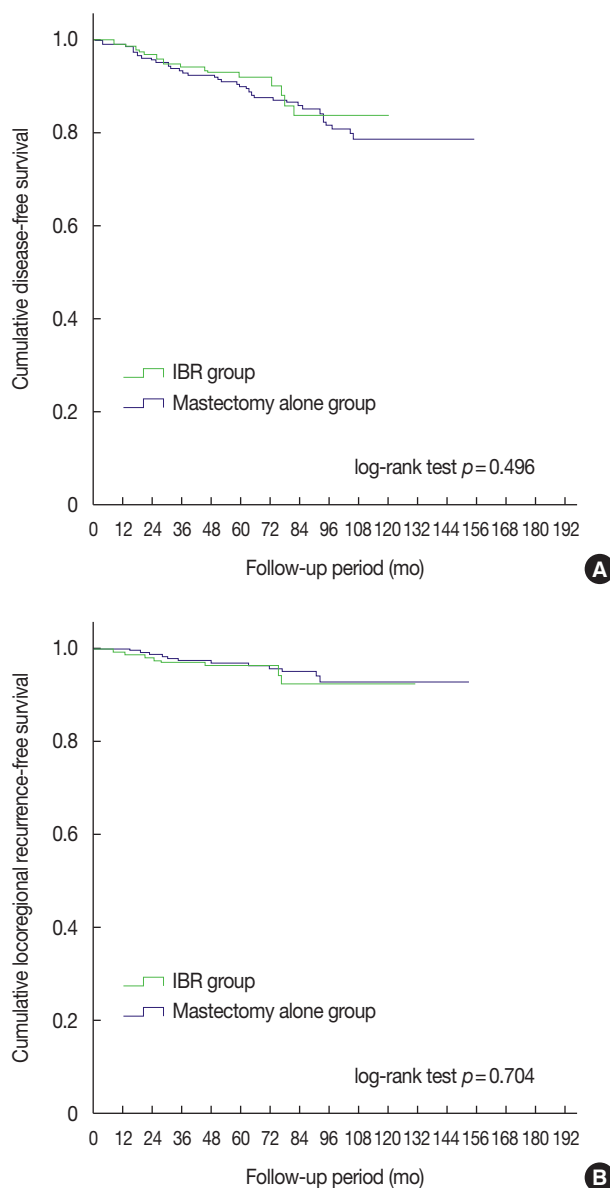
Between 2002 and 2010, 189 patients underwent mastectomy and IBR for invasive breast cancer. A total of 362 patients who underwent conventional mastectomy were matched with those patients based on age, tumor size, axillary lymph node status, ER status, and type of primary treatment. Thus, a total of 551 patients were included in the final analysis. The characteristics of the 551 patients are presented in Table 1. The mean ( $\pm$  standard deviation) age at the time of diagnosis was 41.98 years ( $\pm 80.8$ ) in the IBR group and 45.10 ( $\pm 81.8$ ) years in the mastectomy alone group. Despite controlled matching by age, the IBR group was significantly younger than the mastectomy alone group ( $p = 0.032$ ).

**Table 1.** Patients' characteristics

Characteristic	Study group (n=189) No. (%)	Control group (n=362) No. (%)	p-value
Age (yr)			0.029
<35	43 (22.8)	50 (13.8)	
35–50	116 (61.4)	246 (68.0)	
≥50	30 (15.9)	66 (18.2)	
Tumor stage			0.798
T1	121 (64.0)	216 (59.7)	
T2	52 (27.5)	113 (31.2)	
T3	13 (6.9)	27 (7.5)	
T4	3 (1.6)	6 (1.7)	
Lymph node status			0.864
N0	130 (68.8)	241 (66.6)	
N1	43 (22.8)	86 (23.8)	
N2	9 (4.8)	23 (6.4)	
N3	7 (3.7)	12 (3.3)	
AJCC stage			0.531
I	101 (53.4)	176 (48.6)	
II	66 (34.9)	143 (39.5)	
III	22 (11.6)	43 (11.9)	
ER status			0.846
Positive	129 (68.3)	251 (69.3)	
Negative	60 (31.7)	111 (30.7)	
PR status			0.528
Positive	100 (52.9)	203 (56.1)	
Negative	89 (47.1)	159 (43.9)	
HER2 status			0.005
Not amplified	113 (59.8)	261 (72.1)	
Amplified	55 (29.1)	63 (17.4)	
Equivocal	21 (11.1)	38 (10.5)	
Histologic grade			0.159
Grades 1, 2	10 (5.3)	29 (8.0)	
Grade 3	168 (88.9)	321 (88.7)	
N/A or unknown	11 (5.8)	12 (3.3)	
Ki-67 (%)			0.308
<10	151 (79.9)	281 (77.6)	
≥10	38 (20.1)	81 (22.4)	
Type of primary treatment			0.195
Surgery	344 (95.0)	187 (97.4)	
Chemotherapy	18 (5.0)	5 (2.6)	
Type of reconstruction			N/A
TRAM	151 (79.9)	N/A	
TEI	37 (19.6)	N/A	
LD flap	1 (0.5)	N/A	
Type of mastectomy			N/A
TM	75 (39.7)	362 (100.0)	
SSM	78 (41.3)		
NSM	36 (19.0)		
Adjuvant chemotherapy			0.613
Yes	136 (72.0)	253 (69.9)	
No	53 (28.0)	109 (30.1)	
Adjuvant radiotherapy			0.152
Yes	19 (10.1)	52 (14.4)	
No	170 (89.9)	310 (85.6)	

AJCC=American Joint Committee on Cancer; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; N/A=not available; TRAM=transverse rectus abdominis musculo-cutaneous; TEI=tissue expander insertion; LD=latissimus dorsi; TM=total mastectomy; SSM=skin-sparing mastectomy; NSM=nipple-sparing mastectomy.

T stage, N stage, and American Joint Committee on Cancer (AJCC) stage were not significantly different between the IBR group and mastectomy alone group. In both groups, 11.2% of patients underwent surgery for stage III disease. Neoadjuvant chemotherapy was performed as the primary therapy in five patients (2.6%) in the IBR group and 18 patients (5.0%) in the mastectomy alone group ( $p=0.141$ ). All neoadjuvant chemotherapy patients were clinically stage III. ER status, progester-



**Figure 1.** Recurrence-free survival in all patients. (A) Disease-free survival in the immediate reconstruction group (n=189) and the mastectomy alone group (n=362). (B) Locoregional recurrence-free survival in the immediate reconstruction group (n=189) and the mastectomy alone group (n=362). IBR=immediate breast reconstruction.

**Table 2.** Characteristics of the 18 cases of local recurrence, regional recurrence, distant metastasis in the reconstruction group

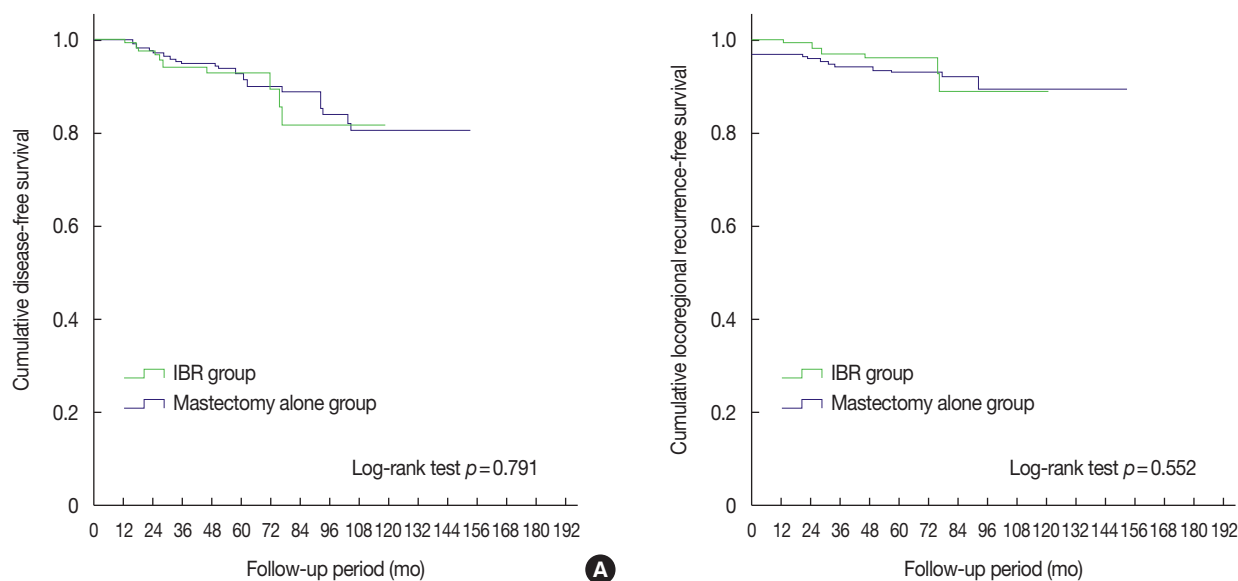
Case	Age (yr)	Mastectomy	Reconstruction	Stage	ER	PR	HER2	NeoCTx	CTx	RTx	Local	Regional	Distant	1st event	Expire
1	44	Modified radical	TRAM	pT2N3M0, IIIC	+	+	-	-	+	-	-	-	Bone	Distant only	Alive
2	32	Modified radical	TRAM	pT2N0M0, IIA	-	-	+	-	-	-	-	-	Bone, lung	Distant only	Alive
3	29	Modified radical	TEI	pT2N0M0, IIA	+	+	-	-	+	-	-	-	Lung	Distant only	Alive
4	28	Modified radical	TEI	pT2N2M0, IIIA	+	+	+	-	-	-	Chest wall	Axilla	Mediastinum	Synchronous	Alive
5	48	Modified radical	TRAM	pT1N1M0, IIA	+	-	-	-	+	-	-	-	Bone, liver	Distant only	Alive
6	39	Modified radical	TRAM	pT2N1M0, IIB	+	-	-	-	+	-	Chest wall	-	Bone, lung, liver	Local first	Alive
7	36	Modified radical	TEI	pT2N0M0, IIA	+	+	-	-	+	-	Chest wall	Supraclavicular LN	Bone, liver	Synchronous	Expire
8	46	Skin-sparing	TRAM	pT1N0M0, IA	+	-	Unknown	-	+	-	Chest wall	Supraclavicular LN	Lung	Synchronous	Alive
9	32	Skin-sparing	TRAM	pT2N1M0, IIB	+	+	-	-	+	-	-	-	Lung	Distant only	Alive
10	41	Skin-sparing	TEI	pT2N1M0, IIB	-	+	-	-	+	-	-	-	Bone	Distant only	Alive
11	33	Skin-sparing	TRAM	pT1N3M0, IIIC	+	-	-	-	+	+	-	-	Bone	Distant only	Expire
12	43	Skin-sparing	TRAM	pT1N3M0, IIIC	+	+	-	-	+	+	-	-	Bone	Distant only	Alive
13	41	Skin-sparing	TRAM	pT3N0M0, IIB	-	-	-	-	+	+	Chest wall	Supraclavicular LN, ipsilateral axill	Bone, lung	Regional first	Expire
14	49	Nipple-sparing	TRAM	pT1N0M0, IA	-	-	+	-	-	-	Skin, nipple	-	-	Local only	Alive
15	42	Nipple-sparing	TRAM	pT1N0M0, IA	-	-	-	-	+	-	Skin, nipple	Subclavicular LN	Bone, lung, liver	Local first	Alive
16	51	Nipple-sparing	TRAM	pT1N1M0, IIA	-	-	+	-	+	-	-	Supraclavicular LN	Bone, lung	Synchronous	Alive
17	46	Nipple-sparing	TRAM	pT2N2M0, IIIA	-	-	-	-	+	-	-	Supraclavicular LN	Liver	Synchronous	Expire
18	34	Nipple-sparing	TRAM	cT4N3M0, IIIC	-	-	+	+	+	-	-	-	Bone, liver	Distant only	Alive

ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; NeoCTx=neoadjuvant chemotherapy; CTx=adjuvant chemotherapy; RTx=adjuvant radiotherapy; TRAM=transverse rectus abdominis musculo-cutaneous; TEI=tissue expander insertion; LN=lymph node.

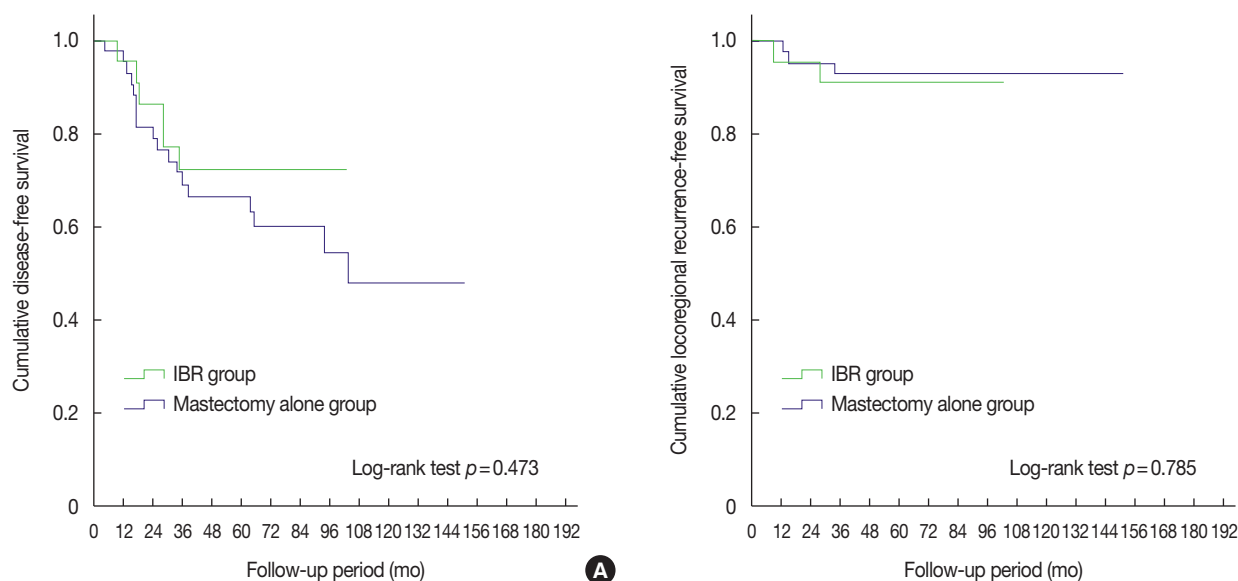
one receptor status, tumor grade, and Ki-67 did not differ between the two groups. However, the IBR group patients had significantly more tumors with human epidermal growth factor receptor 2 (HER2) amplification (29.1% vs. 17.4%,  $p=0.005$ ). The majority of reconstructions were free transverse rectus abdominis flaps (151, 79.9%). Other patients under-

went tissue expander insertion, implant surgery (37, 19.6%), or latissimus dorsi flap reconstruction (1, 0.5%). Of the 189 patients in the IBR group, 75 patients (39.7%) underwent conventional total mastectomy, 78 (41.3%) underwent SSM, and 36 (19.0%) underwent NSM.

The median follow-up durations were 65.6 months (range,



**Figure 2.** Recurrence-free survival in skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) group. (A) Disease-free survival in the immediate reconstruction group with SSM or NSM group ( $n=114$ ) and a matched control group ( $n=191$ ). (B) Locoregional recurrence-free survival in the immediate reconstruction group undergoing either SSM or NSM ( $n=114$ ) and a matched control group ( $n=191$ ). IBR=immediate breast reconstruction.



**Figure 3.** Recurrence-free survival in patients with stage III cancer. (A) Disease-free survival in the immediate reconstruction group with stage III cancer ( $n=22$ ) and a matched control group ( $n=43$ ). (B) Locoregional recurrence-free survival in the immediate reconstruction group with stage III cancer ( $n=22$ ) and a matched control group ( $n=43$ ). IBR=immediate breast reconstruction.

10–132 months) for the IBR group and 81.1 months (range, 1–154 months) for the mastectomy alone group ( $p < 0.001$ ). The overall 5-year survival rates were 97.9% in the IBR group and 97.5% in the mastectomy alone group ( $p = 0.912$ ). During follow-up, 18 patients (9.5%) in the IBR group and 52 patients (14.4%) in the mastectomy alone group experienced recurrence. The characteristics of patients with recurrence in the IBR group are shown in Table 2. There was no significant difference in DFS between the IBR group and mastectomy alone group (5-year DFS, 92.0% and 89.9%, respectively; log-rank test,  $p = 0.496$ ) (Figure 1A). The 5-year LRFS rates were 96.2% and 96.4% for the IBR group and mastectomy alone group, respectively (log-rank test,  $p = 0.704$ ) (Figure 1B). For local recurrence, five patients had recurrences on the chest wall, and two had recurrences on the skin or nipple. All local recurrences were identified by physical examination or routine breast sonography imaging.

We also performed a separate survival analysis for the SSM or NSM group. Between the SSM or NSM group ( $n = 114$ ) and their matched control group ( $n = 191$ ), no significant difference in DFS was found ( $p = 0.791$ ) (Figure 2A). Locoregional recurrence also did not differ between the SSM or NSM group and the matched control group (5-year LRFS, 96.4% and 96.1%, respectively,  $p = 0.552$ ) (Figure 2B). The preoperative distances between the tumor and nipple in the NSM group and control group were 22.5 mm (range, 1–40 mm) and 18.6 mm (range, 1–60 mm), respectively ( $p = 0.186$ ).

Patients with advanced breast cancer (AJCC stage III), including patients who underwent neoadjuvant chemotherapy, were also analyzed as a subgroup. The 5-year DFS rates were not different, at 72.1% and 66.6% in the IBR group and its matched control group, respectively (log-rank test,  $p = 0.473$ ) (Figure 3A). Also, no significant difference in LRFS was found between the two groups (5-year LRFS, 90.9% and 92.7%, respectively; log-rank test,  $p = 0.785$ ) (Figure 3B).

## DISCUSSION

Asian women tend to have smaller and denser breasts compared to those of Western women, which increases patient and surgeons' interests in IBR. Also, the peak incident age in Korea is much younger compared to Western countries, with a median age of 47 to 51 years old [4]. As a result of this younger patient group, obtaining acceptable cosmetic results along and oncologic safety are important issues in treating breast cancer patients. However, there are fewer reports on the oncologic safety of IBR in Asia compared to Western countries, and these studies also lack a variable-based matched control group [1,11,12]. In this retrospective study, we per-

formed a matched case-control study, adjusting for factors related to survival outcomes in order to reduce selection bias of patients undergoing mastectomy and IBR. We demonstrated the oncologic safety of IBR after curative surgery for invasive breast cancer patients, reporting no differences in OS, DFS, and LRFS between the two groups, regardless of the type of mastectomy or cancer stage.

We have demonstrated comparable oncologic safety in a subgroup of patients who underwent SSM or NSM. Previous studies have reported that the remaining extra skin after SSM contains residual breast tissue in almost 60% of cases [3,13]. However, the average weight of the residual breast tissue in SSM was found to be a mere 0.02% of the total removed tissue [3,14]. Additionally, Doddi et al. [15] indicated that locoregional recurrence after IBR cannot be affected by inadequate excision alone, but it is more affected by other prognostic factors. Many previous reports found similar results to those in our study, demonstrating no difference between SSM or NSM and conventional mastectomies [8,9,11,12,16].

The oncologic safety of IBR in advanced-stage disease or after neoadjuvant chemotherapy is still debatable. Most studies showed no increase in recurrence rates of advanced-stage tumors [17–20]. However, Mallon et al. [21] reported a significant increase in the locoregional recurrence rate of patients with non-endocrine responsive breast cancer undergoing IBR after neoadjuvant chemotherapy, and Murthy and Chamberlain [22] reported a relatively high distant metastasis rate after total SSM in patients with locally advanced disease. In our study, there were no differences in DFS and LRFS between advanced-stage breast cancer patients who underwent mastectomy and IBR compared to those who underwent mastectomy alone, consistent with the results of the majority of previous reports.

Another concern about IBR is that it can interfere with local recurrence detection [1,23]. Many patients hesitate to proceed with IBR due to anxiety over the possibility of missing a local recurrence diagnosis due to the reconstructed breast. However, most local recurrences in a reconstructed breast occur at the skin level, allowing detection by physical examination [10, 13,24,25]. Additionally, support from imaging modalities can allow tumor recurrence detection prior to clinical presentation [26]. In our study, all local recurrences were detected by physical examination or breast sonography.

Despite controlled matching within three age groups, patients who underwent IBR were younger than patients in the mastectomy alone group (median age, 41.98 vs. 45.10 years,  $p = 0.032$ ). This difference has been repeatedly demonstrated in almost all previous studies [7]. Although breast reconstruction must be offered despite age, surgeons have a tendency to

propose it to younger patients or to patients without other comorbidities. Additionally, younger patients are more likely to seek breast reconstruction to achieve better cosmetic results.

The retrospective nature of our study is a major limitation. To overcome it, we have performed a matched case-control study analysis, but accurate evaluation of oncologic safety is still limited. Moreover, we did not include all prognostic factors among the matching variables. We excluded such prognostic factors as tumor grade, HER2 status, and Ki-67. Many cases were missing these data, and thus, including them would have led to a decrease in the number of matched control cases and analysis efficiency. However due to this exclusion, patients in the IBR group had more tumors with HER2 amplification (29.1% vs. 17.4%,  $p=0.005$ ). In spite of this difference, no difference in survival was observed between the two groups. Another limitation is the length of time over which we drew our patient cohort. Any changes in therapeutic strategies or regimens in this long period could influence the final results related to oncologic safety comparisons. Finally, the median follow-up duration of the IBR group was significantly shorter than that of the mastectomy alone group (65.62 months vs. 81.12 months, respectively;  $p<0.001$ ), exposing the possibility of a length of time bias.

In conclusion, mastectomy and IBR had no negative impact on recurrence or patient survival, even in patients who underwent SSM or NSM and patients with advanced breast cancer. Locoregional recurrence rates were acceptable for patients who underwent skin-sparing procedures or had advanced-stage disease. Therefore, patients can continue to have IBR without worrying about increased recurrence or late detection of locoregional recurrence.

## CONFLICT OF INTEREST

The authors declare that they have no competing of interests.

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