

## Original Article



# Immediate Breast Reconstruction Does Not Have a Clinically Significant Impact on Adjuvant Treatment Delay and Subsequent Survival Outcomes

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### Conflict of Interest

The authors have declared that they have no competing interests.

## ABSTRACT

**Purpose:** The use of immediate breast reconstruction (IBR) has been debated because it may be a causative factor in adjuvant treatment delay and may subsequently increase the probability of recurrence. We investigated whether IBR was related to adjuvant treatment delay and survival outcomes.

**Methods:** We retrospectively analyzed the duration from operation to adjuvant treatment administration and survival outcomes according to IBR status among patients with breast cancer who underwent mastectomy followed by adjuvant chemotherapy from January 2005 to December 2014. Propensity score matching was performed to balance the clinicopathologic baseline characteristics between patients who did and did not undergo IBR.

**Results:** Of 646 patients, 107 (16.6%) underwent IBR, and the median follow-up was 72 months. The median duration from surgery to adjuvant chemotherapy was significantly longer in patients who underwent IBR than in those who did not (14 vs. 12 days, respectively,  $p = 0.008$ ). Based on propensity score matching, patients who underwent IBR received adjuvant therapy 3 days later than those who did not (14 vs. 11 days, respectively,  $p = 0.044$ ). The duration from surgery to post-mastectomy radiation therapy (PMRT) did not significantly differ between the 2 groups. Local recurrence-free survival, regional recurrence-free survival, systemic recurrence-free survival, and overall survival were also not significantly different between the 2 groups ( $p = 0.427$ ,  $p = 0.445$ ,  $p = 0.269$ , and  $p = 0.250$ , respectively). In the case-matched cohort, survival outcomes did not change.

**Conclusion:** IBR was associated with a modest increase in the duration from surgery to chemotherapy that was statistically but not clinically significant. Moreover, IBR had no influence on PMRT delay or survival outcomes, suggesting that it is an acceptable option for patients with non-metastatic breast cancer undergoing mastectomy.

**Keywords:** Breast implants; Breast neoplasm; Chemotherapy, adjuvant; Radiotherapy, adjuvant; Recurrence

**Author Contributions**

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**INTRODUCTION**

Despite advances in diagnosis and treatment, about 45% of all patients with breast cancer still undergo mastectomy to achieve adequate local control [1,2]. Owing to poor cosmetic outcomes, patients who undergo mastectomy are less satisfied after surgery than those who undergo breast-conserving surgery [3-5]. Consequently, the use of breast reconstruction after mastectomy has increased in patients with breast cancer [6], and, in Korea, the performance of mastectomy followed by breast reconstruction increased threefold between 2002 and 2013 [7]. When first introduced, breast reconstruction was generally performed after the completion of additional adjuvant treatment, including chemotherapy and radiotherapy, but the rate of immediate breast reconstruction (IBR) has recently increased because of its various advantages, such as relieving emotional stress, avoiding additional operations, reducing costs, and providing favorable cosmetic outcomes [8,9].

However, there is concern that the performance of IBR delays administration of adjuvant treatment, which may negatively impact survival outcomes. Previous research has shown that the incidence of postoperative complications was higher in patients who underwent IBR than in those who underwent mastectomy alone, a factor that may increase the time to adjuvant treatment or even result in its omission [10,11]. Moreover, several studies have reported that the delay of adjuvant treatment is associated with poor survival rates in patients with breast cancer [12,13]. In contrast, other studies have suggested that a modest delay in adjuvant treatment is unlikely to have any clinical significance, even though IBR is associated with a statistically significant delay in the initiation of chemotherapy [14]. To date, the studies that have examined IBR and its impact on the initiation of adjuvant treatment and survival outcomes in patients with breast cancer have yielded conflicting results.

The purpose of the present study was to determine the impact of IBR on adjuvant treatment administration and subsequent survival outcomes. We compared the duration from surgery to adjuvant treatment, including chemotherapy and post-mastectomy radiation therapy (PMRT), and survival rates according to whether or not IBR was performed.

**METHODS****Patients**

From January 1, 2005, to December 31, 2014, 731 patients with invasive breast cancer underwent mastectomy, including conventional total mastectomy, skin sparing mastectomy, and nipple-areola complex sparing mastectomy, followed by chemotherapy at the Gangnam Severance Hospital. We excluded patients based on the following criteria: i) *de novo* stage IV cancer, ii) recurrent breast cancer, iii) history of neoadjuvant chemotherapy, or iv) history of delayed breast reconstruction. Finally, retrospective analysis was performed on a total of 646 women. IBR was defined as breast reconstruction performed by plastic surgeons concurrently with mastectomy. The method of breast reconstruction in each case, such as permanent implant, tissue expander, or autologous reconstruction, was determined by plastic surgeons considering the anticipated adjuvant treatment, physical presentation, and preference of patients. Clinicopathologic data, including age at surgery, histologic grade, lymphovascular invasion, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor 2 (HER2) status, Ki-67 levels, pathologic T stage, and pathologic N stage, were recorded. TNM stage was determined using the 7th edition of the

American Joint Committee on Cancer staging manual. Treatment information, including IBR status, chemotherapy regimen, and PMRT, was examined.

In accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, our study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University, Seoul, Republic of Korea (IRB No. 3-2018-0215). The requirement for informed consent was waived owing to the retrospective study design.

### Study outcomes

The primary outcomes were the impact of IBR on adjuvant treatment delay and survival rates, including local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), systemic recurrence-free survival (SRFS), and overall survival (OS). The impact of IBR on delay of adjuvant treatment was determined by comparing the duration from surgery to the initiation of adjuvant treatment according to whether or not IBR was performed. LRFS, RRFS, and SRFS were calculated from the date of mastectomy to the date of first local, regional, and systemic recurrence, respectively. OS was calculated as the duration from the date of mastectomy to death or the last date of study follow-up (May 31, 2018).

### Statistical analysis

Continuous variables were compared using Student's *t*-test. Discrete variables were compared using the  $\chi^2$  test or Fisher's exact test. Durations from surgery to adjuvant chemotherapy and PMRT administration were estimated using Kaplan-Meier estimates with the log-rank test. The Kaplan-Meier method was used to estimate LRFS, RRFS, SRFS, and OS, and the estimated survival curves were compared using the log-rank test.

We performed an individual propensity score matching analysis in which randomly selected patients who underwent IBR were paired with comparable patients who did not undergo IBR. The selection of one case per 2 controls was based on age; histologic grade; ER, PR, and HER2 status; pathologic stage; chemotherapy regimen; and PMRT. All analyses were performed using SPSS version 23 (IBM Corp., Armonk, USA) and SAS (version 9.3, SAS Inc., Cary, USA). Statistical significance was defined by a *p*-value < 0.05.

## RESULTS

### Baseline characteristics

A total of 646 patients with stage I–III breast cancer who underwent mastectomy followed by adjuvant chemotherapy at the Gangnam Severance Hospital from January 2005 to December 2014 were included in the present study. Baseline characteristics are listed in **Table 1**. The median patient age was 50 (range, 28–82) years. There were 291 (45.0%) ER-negative and 224 (35.3%) HER2-positive patients. Stage II disease was the most common (407 patients, 63.0%), and 152 (23.5%) patients received PMRT after adjuvant chemotherapy.

A total of 107 (16.6%) patients underwent IBR (IBR group). Of these, 68 (63.6%) patients underwent conventional total mastectomy, 21 (19.6%) patients underwent skin sparing mastectomy, and 18 (16.8%) patients underwent nipple-areola complex sparing mastectomy. In addition, a permanent implant was used in 27 (25.2%) patients, a tissue expander in 26 (24.3%), a transverse rectus abdominis myocutaneous flap in 43 (40.2%), and a latissimus dorsi muscle flap in 11 (10.3%). In contrast, conventional total mastectomy was performed

**Table 1.** Clinicopathologic baseline characteristics in all patients and case-matched cohort

Variable	All patients, No. (%)			p-value	Case-matched cohort, No. (%)			p-value
	No IBR (n = 539)	IBR (n = 107)	Total (n = 646)		No IBR (n = 178)	IBR (n = 89)	Total (n = 267)	
Age (yr)*	50 (28-82)	50 (30-67)	50 (28-82)	0.053	50 (28-76)	50 (32-67)	50 (28-76)	0.563
Histology				0.208 <sup>‡</sup>				0.059
IDC	518 (96.1)	99 (92.5)	617 (95.5)		175 (98.3)	84 (94.4)	259 (97.0)	
ILC	12 (2.2)	4 (3.7)	16 (2.5)		3 (1.7)	3 (3.4)	6 (2.2)	
Others	9 (1.7)	4 (3.7)	13 (2.0)		0	2 (2.2)	2 (0.7)	
HG <sup>†</sup>				0.039				0.465
1 or 2	343 (67.7)	81 (77.9)	424 (69.4)		141 (79.2)	67 (75.3)	208 (77.9)	
3	164 (32.3)	23 (22.1)	187 (30.6)		37 (20.8)	22 (24.7)	59 (22.1)	
LVI <sup>†</sup>				0.122				0.126
No	353 (73.4)	63 (65.6)	416 (72.1)		123 (75.9)	54 (66.7)	177 (72.8)	
Yes	128 (26.6)	33 (34.4)	161 (27.9)		39 (24.1)	27 (33.3)	66 (27.2)	
ER				0.001				0.855
Positive	281 (52.1)	74 (69.2)	355 (55.0)		118 (66.3)	58 (65.2)	176 (65.9)	
Negative	258 (47.9)	33 (30.8)	291 (45.0)		60 (33.7)	31 (34.8)	91 (34.1)	
PR <sup>†</sup>				0.008				> 0.999
Positive	271 (51.3)	70 (65.4)	341 (53.7)		110 (61.8)	55 (61.8)	165 (61.8)	
Negative	257 (48.7)	37 (34.6)	294 (46.3)		68 (38.2)	34 (38.2)	102 (38.2)	
HER2 <sup>†</sup>				0.292				0.576
Positive	191 (36.2)	33 (30.8)	224 (35.3)		58 (32.6)	26 (29.2)	84 (31.5)	
Negative	337 (63.8)	74 (69.2)	411 (64.7)		120 (67.4)	63 (70.8)	183 (68.5)	
Ki-67 (%) <sup>†</sup>				0.656				0.928
< 14	326 (61.7)	63 (59.4)	389 (61.4)		113 (63.5)	56 (62.9)	169 (63.3)	
≥ 14	202 (38.3)	43 (40.6)	245 (38.6)		65 (36.5)	33 (37.1)	98 (36.7)	
T stage				0.094 <sup>‡</sup>				0.397 <sup>‡</sup>
1	208 (38.6)	55 (51.4)	50 (53.2)		72 (40.4)	43 (48.3)	115 (43.1)	
2	307 (57.0)	50 (46.7)	42 (44.7)		103 (57.9)	45 (50.6)	148 (55.4)	
3	20 (3.7)	2 (1.9)	2 (2.1)		1 (0.6)	1 (1.1)	2 (0.7)	
4	4 (0.7)	0	4 (0.6)		2 (1.1)	0	2 (0.7)	
N stage				0.143				0.409
0	266 (49.4)	53 (49.5)	319 (49.4)		92 (51.7)	41 (46.1)	133 (49.8)	
1	190 (35.3)	45 (42.1)	235 (36.4)		66 (37.1)	40 (44.9)	106 (39.7)	
2	55 (10.2)	8 (7.5)	63 (9.8)		13 (7.3)	7 (7.9)	20 (7.5)	
3	28 (5.2)	1 (0.9)	1 (0.9)		7 (3.9)	1 (1.1)	8 (3.0)	
Stage				0.071				0.673
1	113 (21.0)	29 (27.1)	142 (22.0)		42 (23.6)	19 (21.3)	61 (22.8)	
2	338 (62.7)	69 (64.5)	407 (63.0)		115 (64.6)	62 (69.7)	177 (66.3)	
3	88 (16.3)	9 (8.4)	97 (15.0)		21 (11.8)	8 (9.0)	29 (10.9)	
Chemotherapy				0.084				0.983
CMF	16 (3.0)	0	16 (2.5)		-	-	-	
AC	228 (42.3)	54 (50.5)	282 (43.7)		85 (47.8)	43 (48.3)	128 (47.9)	
AC-T	246 (45.6)	48 (44.9)	294 (45.5)		82 (46.1)	41 (46.1)	123 (46.1)	
Others	49 (9.1)	5 (4.7)	54 (8.4)		11 (6.2)	5 (5.6)	16 (6.0)	
Not done	-	-	-		-	-	-	
PMRT				0.297				0.509
Done	131 (24.3)	21 (19.6)	152 (23.5)		36 (20.2)	15 (16.9)	51 (19.1)	
Not done	408 (75.7)	86 (80.4)	494 (76.5)		142 (79.8)	74 (83.1)	216 (80.9)	

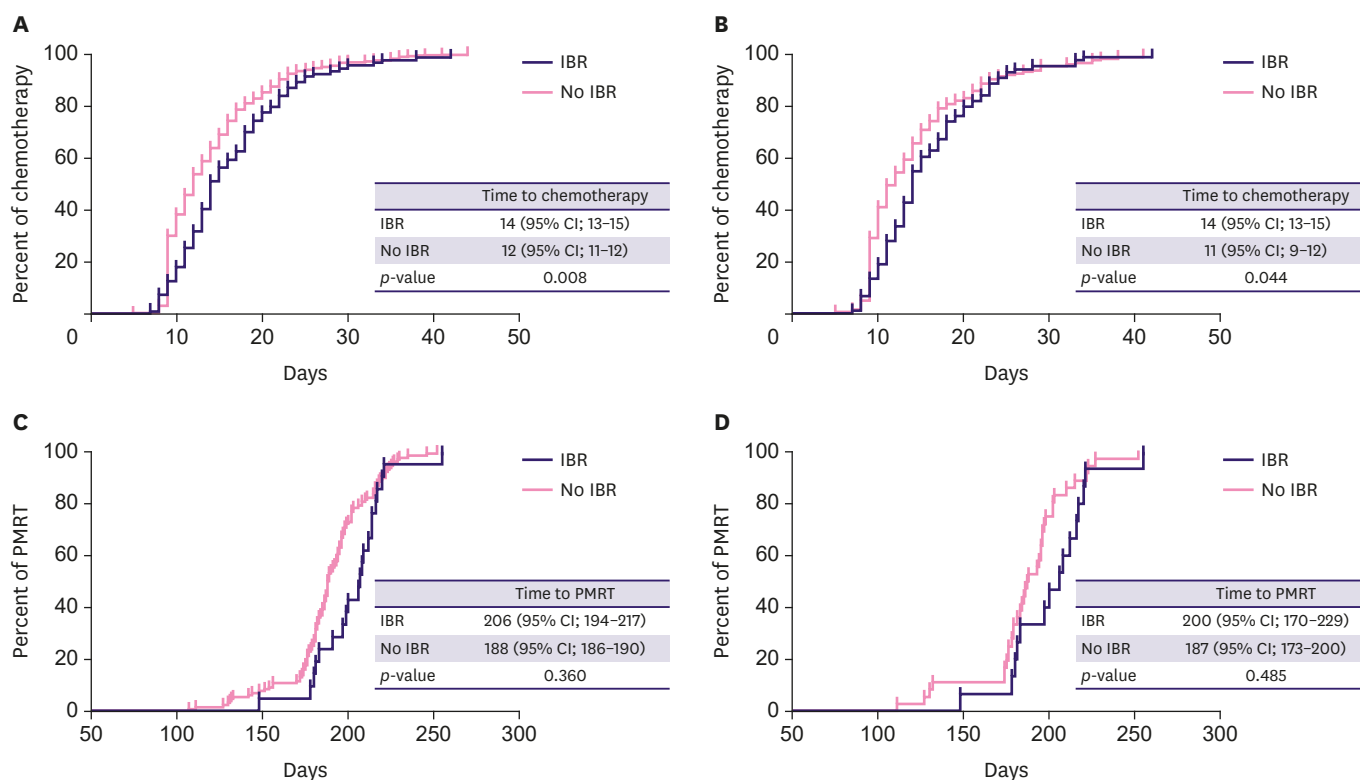
IBR = immediate breast reconstruction; IDC = invasive ductal cancer; ILC = invasive lobular cancer; HG = histologic grade; LVI = lymphovascular invasion; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; AC = doxorubicin and cyclophosphamide; AC-T = doxorubicin and cyclophosphamide followed by taxane; PMRT = post-mastectomy radiation therapy  
\*Median(range); †Missing values; ‡Fisher's exact test.

in all patients who did not undergo IBR. Patients in the IBR group were significantly more likely to have low histologic grade and ER- and PR-positive tumors than those who did not undergo IBR (no IBR group) (**Table 1**). In addition, patient age and pathologic tumor stage tended to be lower in the IBR group than in the no IBR group, but these differences were not statistically significant. In node-positive patients, IBR was more likely to be performed if tumors were ER- or PR-positive and low pathologic stage (**Supplementary Table 1**). After

propensity score matching, a total of 267 patients were included. Of these, 89 (33.3%) patients underwent IBR. Clinicopathologic baseline characteristics were well balanced between patients according to IBR status (**Table 1**).

### Delay of adjuvant treatment

Overall, the duration from surgery to adjuvant chemotherapy ranged from 4 to 44 days, and the duration from surgery to adjuvant radiotherapy ranged from 107 to 255 days. Adjuvant chemotherapy was performed within 3 months in all patients, and within 30 days in a large majority of patients (622 of 646 patients, 96.3%). Among patients with a duration from surgery to adjuvant chemotherapy exceeding 30 days, 5 (4.7%) were in the IBR group and 19 (3.5%) were in the no IBR group ( $p = 0.782$ ). Differences in the duration from surgery to adjuvant chemotherapy and PMRT were compared according to IBR status. The median duration from surgery to adjuvant chemotherapy in the IBR group was significantly longer than the median duration in the no IBR group (14 days, range 7–42 days vs. 12 days, range 4–44 days, respectively,  $p = 0.008$ ; **Figure 1A**). The median duration from surgery to adjuvant chemotherapy was also significantly longer in the IBR group in the case-matched cohort (14 days, range 7–42 days vs. 11 days, range 5–41 days, respectively,  $p = 0.044$ ; **Figure 1B**). In node-positive patients, adjuvant chemotherapy was initiated 3 days later in the IBR group than in the no IBR group, but this difference was not statistically significant (15 days, range 8–25 days vs. 12 days, range 4–44 days, respectively,  $p = 0.060$ ; **Supplementary Figure 1A**). However, analysis of the entire patient sample revealed that the median duration from surgery to PMRT was not significantly different between the 2 groups based on IBR status (IBR group: 206 days, range 148–255 days vs. no IBR group: 188 days, range 107–252 days,  $p = 0.360$ ; **Figure 1C**). Similar results were observed in the case-matched



**Figure 1.** Impact of IBR on adjuvant treatment. Duration from surgery to adjuvant chemotherapy (A) in all patients and (B) in a case-matched cohort duration. Duration from surgery to PMRT (C) in all patients and (D) in a case-matched cohort duration. IBR = immediate breast reconstruction; PMRT = post-mastectomy radiation therapy; CI = confidence interval.

**Table 2.** Survival outcomes in all patients and case-matched cohort

Variable	All patients, No. (%)			p-value	Case-matched cohort, No. (%)			p-value
	No IBR (n = 539)	IBR (n = 107)	Total (n = 646)		No IBR (n = 178)	IBR (n = 89)	Total (n = 267)	
Local recurrence				0.625*				0.333*
No	535 (98.9)	105 (98.1)	638 (98.8)		178 (100.0)	88 (98.9)	266 (99.6)	
Yes	6 (1.1)	2 (1.9)	8 (1.2)		0	1 (1.1)	1 (0.4)	
Regional recurrence				0.461*				0.337*
No	529 (98.1)	104 (97.2)	633 (98.0)		176 (98.9)	86 (96.6)	262 (98.1)	
Yes	10 (1.9)	3 (2.8)	13 (2.0)		2 (1.1)	3 (3.4)	5 (1.9)	
Systemic recurrence				0.474				0.753
No	465 (91.8)	96 (89.7)	591 (91.5)		164 (92.1)	81 (91.0)	245 (91.8)	
Yes	44 (8.2)	11 (10.3)	55 (8.5)		14 (7.9)	8 (9.0)	22 (8.2)	
Death				0.179				> 0.999
No	521 (96.7)	106 (99.1)	627 (97.1)		176 (98.9)	88 (98.9)	264 (98.9)	
Yes	18 (3.3)	1 (0.9)	19 (2.9)		2 (1.1)	1 (1.1)	3 (1.1)	

IBR = immediate breast reconstruction.

\*Fisher's exact test

cohort (IBR group: 200 days, range 148–255 days vs. no IBR group: 187 days, range 111–252 days,  $p = 0.485$ ; **Figure 1D**) and in node-positive patients (IBR group: 200 days, range 148–2255 days vs. no IBR group: 189 days, range 131–252 days,  $p = 0.647$ ; **Supplementary Figure 1B**).

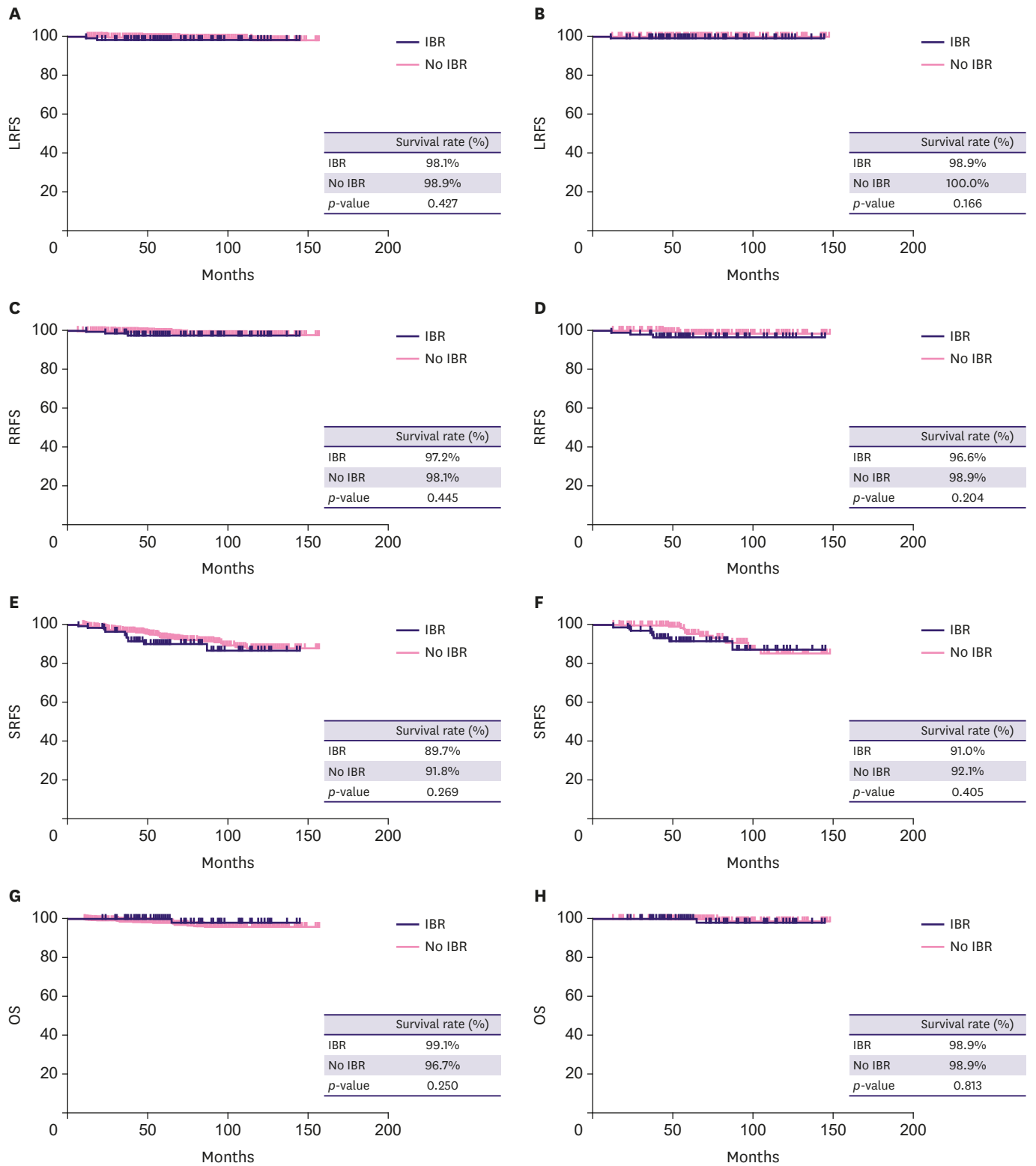
### Survival outcomes

During the median follow-up period of 72 (1–157) months, 76 (11.8%) recurrence events occurred, including 8 (1.2%) local recurrences, 13 (2.0%) regional recurrences, and 55 (8.5%) systemic recurrences (**Table 2**). In addition, 19 (2.9%) deaths occurred. LRFs, RRFs, SRFs, and OS did not significantly differ according to IBR status when the entire patient group was analyzed ( $p = 0.427$ ,  $p = 0.445$ ,  $p = 0.269$ , and  $p = 0.250$ , respectively, by log-rank test; **Figure 2**). Similarly, the survival outcomes were not significantly different in either the case-matched cohort (**Figure 2**) or node-positive patients (**Supplementary Figure 2**).

## DISCUSSION

In the present study, we evaluated whether performance of IBR delayed administration of adjuvant treatment and negatively affected subsequent survival outcomes. The median time from surgery to adjuvant chemotherapy in the IBR group was significantly longer than that in the no IBR group. However, adjuvant chemotherapy was delayed for only 2–3 days in the IBR group compared to the delay in the no IBR group. On the other hand, whether or not IBR was performed was not related to delay in PMRT administration. Finally, survival outcomes, including LRFs, RRFs, SRFs, and OS, did not significantly differ according to IBR status, a finding similar to the results of previous studies [15–17].

When IBR was first introduced, the procedure was less likely to be performed in patients with high disease stage or poor prognostic factors because of lack of data regarding its oncologic safety [18,19]. Therefore, IBR was initially recommended for patients with stage 0–II disease with relatively low likelihood of metastasis and postoperative complications. Correspondingly, in the present study, patients in the IBR group had a higher number of good prognostic factors than those in the no IBR group. For this reason, we used propensity score matching to adjust for confounding factors according to IBR status. Additionally, subanalysis was performed in node-positive patients to investigate whether IBR influenced adjuvant treatment delay or survival outcomes in patients with locally advanced breast cancer.



**Figure 2.** Impact of IBR on survival outcomes. LRFS (**A**) in all patients and (**B**) in a case-matched cohort. RRFs (**C**) in all patients and (**D**) in a case-matched cohort. SRFS (**E**) in all patients and (**F**) in a case-matched cohort. OS (**G**) in all patients and (**H**) in a case-matched cohort. IBR = immediate breast reconstruction; LRFS = local recurrence-free survival; RRFs = regional recurrence-free survival; SRFS = systemic recurrence-free survival; OS = overall survival.



In both the case-matched cohort and node-positive patients, no clinically significant delay of adjuvant treatment or difference in survival outcomes was observed according to IBR status. To our knowledge, there have been no previous studies using propensity score matching to balance the baseline characteristics according to IBR status, and analyzing adjuvant treatment delay and the details of survival outcomes in terms of local, regional, and systemic recurrence, and OS. This unique approach is the major strength of our study.

Numerous studies have attempted to identify a cut-off point for the duration from surgery to adjuvant chemotherapy that decreases survival in patients with breast cancer undergoing IBR. However, no such cut-off point has been identified, provided that chemotherapy is initiated within 3 months after mastectomy with IBR [20,21]. Moreover, several studies have recommended that adjuvant chemotherapy be initiated within 12 weeks after primary surgery, at the latest, to guarantee oncologic safety [22,23]. In the present study, the median time from surgery to chemotherapy was 14–15 days for patients who underwent IBR, a period only 2–3 days longer than the median time for patients who underwent mastectomy only. The longest duration from surgery to adjuvant chemotherapy in any patient undergoing IBR in the present study was 42 days, a duration still within 12 weeks. Therefore, it appeared that the delay of adjuvant chemotherapy in the IBR group as compared to that in the no IBR group was unlikely to have any clinical significance.

PMRT has traditionally been administered to patients with breast cancer with tumors > 5 cm or those with 4 or more involved axillary lymph nodes [24]. In the past decade, however, the indications for PMRT have expanded because several trials have revealed that PMRT decreased locoregional recurrence in patients with 1–3 positive lymph nodes [25,26]. The National Comprehensive Cancer Network expanded its treatment guidelines to “strongly consider” PMRT for patients with tumors ≤ 5 cm and 1–3 positive lymph nodes [27]. In the present study, 21 (19.6%) of 107 patients who underwent IBR received PMRT. Of these 21 patients, 9 (42.9%) had tumors > 5 cm or 4 or more involved axillary lymph nodes, and 12 (57.1%) had tumors ≤ 5 cm and 1–3 positive axillary lymph nodes. As the indications for PMRT have expanded, there has been growing concern that delay in administration of radiation therapy is associated with inferior survival outcomes. Nevertheless, most studies investigating the role of PMRT in patients undergoing IBR have focused on cosmesis, not survival outcomes. A few studies have demonstrated that IBR did not delay PMRT administration [28,29]. Similarly, the median duration from surgery to initiation of PMRT was not significantly different in the present study according to whether or not a patient underwent IBR. However, further research regarding the effect of IBR on PMRT delay and the subsequent survival rate is needed with a larger cohort.

The current study has some limitations. The rate of postoperative complications could not be evaluated in this study owing to the retrospective design, although the postoperative complications in patients who underwent IBR were major reasons to postpone adjuvant treatment [10]. In addition, we were unable to analyze the duration from diagnosis to surgery. Difficulties in planning a multidisciplinary surgery such as IBR are among the factors that delay initiation of surgery and adjuvant treatment [30]. Jabo et al. [29] reported a significantly lower survival when the period from diagnosis to surgery exceeded 120 days. It was difficult to record the exact date of diagnosis in our study, because many patients were initially diagnosed at other hospitals. Finally, the effect of IBR on the delay of adjuvant treatment and survival rates according to type of mastectomy, such as nipple-areola complex sparing mastectomy and skin sparing mastectomy, and the method of IBR were not



investigated. Further studies examining these limitations are warranted to determine the exact impact of IBR on adjuvant treatments and subsequent survival outcomes.

In conclusion, IBR was associated with a modest increase in the duration from surgery to chemotherapy that was statistically but not clinically significant. Moreover, IBR did not delay adjuvant radiotherapy or negatively impact survival outcomes. These results did not change after propensity score matching to balance the clinicopathologic factors according to whether or not IBR was performed. Therefore, the present study suggested that IBR is a valid option for patients with non-metastatic breast cancer undergoing mastectomy.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Clinicopathologic baseline characteristics in node positive patients

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### Supplementary Figure 1

Impact of IBR on adjuvant treatment in node-positive breast cancer patients. (A) Duration from surgery to adjuvant chemotherapy and (B) duration from surgery to PMRT.

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### Supplementary Figure 2

Impact of IBR on survival outcomes in node-positive breast cancer patients. (A) LRFS, (B) RRFS, (C) SRFS, and (D) OS duration according to IBR status.

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