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Original Article

Impact of Immediate Breast Reconstruction on Survival of Breast Cancer Patients: A Single-Center Observational Study

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Although immediate breast reconstruction following mastectomy has become increasingly common, its oncological safety has been debated. We enrolled patients with breast cancer who underwent surgery at Okayama University Hospital between 2007 and 2013. The primary outcome was relapse-free survival (RFS). Secondary outcomes were overall survival and the duration from the surgery to the initiation of adjuvant chemotherapy. We divided into immediate breast reconstruction, mastectomy alone, and breast conservative surgery groups. Outcomes were compared using Cox's regression analysis. A total of 614 patients were included (reconstruction: 125, mastectomy: 128, breast conservative surgery: 361). The median follow-up duration was 79.0±31.9 months. The immediate-reconstruction patients were younger, had more lymph node metastases, and more often received postoperative chemotherapy. The RFS was better after the breast conservative surgery compared to after reconstruction (hazard ratio 0.33, 95% confidence interval: 0.144-0.763). The proportion of local recurrence was highest in the reconstruction group. No patients in the reconstruction group underwent postoperative radiation therapy. However, reconstruction did not affect overall survival or the time to the initiation of adjuvant chemotherapy. Surgeons should explain the risks of breast reconstruction to their patients preoperatively. Careful long-term follow-up is required after such procedures.

Key words: immediate breast reconstruction, oncological safety, local recurrence, postoperative radiation therapy, time to initiation of adjuvant chemotherapy

Breast cancer is the most common cancer among women, with approx. 2.1 million women diagnosed worldwide each year [1]. In Japan, the age-adjusted incidence of breast cancer is the highest among all women's cancers, but the age-adjusted death rate for patients with breast cancer ranks fifth among cancers overall [2]. This indicates the existence of many survivors of breast cancer.

Immediate breast reconstruction following mastectomy (IBR) has become more common. IBR is associated with several benefits, including maintaining the

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patient's body image, improved sexuality and sense of femininity, and other positive effects on patients' psychological well-being and quality of life [3-6]. In recent years there has been an increase in the number of patients indicated for breast conservative surgery (BCS) who wish to undergo IBR due to concerns regarding postoperative breast deformity.

Although IBR plays an important role in the management of breast cancer, its postoperative oncological safety has been a controversial topic. Because the residual skin envelope may contain occult cancer cells that can lead to future relapse [7, 8], inserting a flap or silicone breast implant between the chest wall and breast skin envelope may mask local recurrence and impair the ability to detect residual cancer cells [7]. In addition, patients who have undergone a mastectomy should be encouraged to start adjuvant chemotherapy within 12 weeks after the surgery, as exceeding this window can compromise relapse-free survival (RFS) and overall survival (OS) [9, 10]. Some studies have reported that patients who undergo IBR have a higher incidence of surgical-site complications and infections versus those who undergo a mastectomy alone [11, 12], and these postoperative complications may delay the administration of adjuvant chemotherapy.

However, many previous studies identified no significant differences in survival between patients who underwent IBR and those who underwent a mastectomy alone [7, 13-19]. Few studies have compared oncological outcomes among IBR, mastectomy alone, and BCS. Comparing such outcomes will provide useful information for future surgical candidates. We conducted the present study to assess the impact of IBR on oncological outcomes (focusing on RFS and OS) and to compare the duration between surgery and the initiation of adjuvant chemotherapy among patients who have undergone IBR, mastectomy alone, or BCS.

Patients and Methods

Study patients. We obtained the patients' information from the Setouchi Breast Cancer Registry database, which is a registry project operated by the Setouchi Breast Project Support Organization and contains information from 50 breast cancer centers. The objective of the Registry is to standardize breast cancer treatment, collect epidemiological information, and aid clinical research [2]. The following patient information was gathered and evaluated: age, body mass index, menstrual information, tumor size, lymph node metastasis, pathological tumor stage, the use/non-use of adjuvant chemotherapy and the duration (days) to its initiation, lymphovascular invasion, nuclear grade, levels of three biomarkers (estrogen receptor [ER], progesterone receptor [PgR], and human epidermal growth factor receptor 2 [HER-2]), follow-up duration, surgical procedure (IBR, mastectomy alone, BCS), recurrence (local, regional, and distant, duration from surgery to recurrence, cause of death, and duration from surgery to death.

We included all patients who underwent breast cancer surgery at Okayama University Hospital between August 2007 and December 2013. Patients who received neoadjuvant chemotherapy, those scheduled for delayed reconstruction or prophylactic mastectomy, those < 20 years old, and those diagnosed with bilateral breast cancer, clinical stage IV, secondary cancer, or breast cancer recurrence were excluded.

We divided the patients into three groups: the IBR, mastectomy alone (hereafter "mastectomy"), and BCS groups. A deep inferior epigastric artery perforator flap, transverse rectus abdominis musculocutaneous flap, latissimus dorsi myocutaneous flap, and silicone breast implant following tissue expander surgery were included as reconstructions. When the patient declared a preference for reconstruction, the breast surgeon provided a referral to a plastic surgeon who explained the benefits and disadvantages of reconstruction preoperatively. When selecting the surgical procedure, surgeons attempted to adhere to the patient's wishes as much as possible.

Patients were followed up by both breast and plastic surgeons depending on the degree of postoperative wound recovery and treatment needs. The necessity of adjuvant therapy was determined according to the guidelines of the Japanese Breast Cancer Society [20]. For example, both IBR and mastectomy with four or more lymph node metastases or with a tumor size ≥ 5 cm were considered indications for postoperative radiation therapy (PMRT). All of the patients who underwent BCS also received PMRT. The use of postoperative chemotherapy was determined based on the tumor size, the presence of axillary lymph node metastasis, and the estimated risk of based on pathological factors.

This study was approved by the Ethics Committee of

Okayama University Hospital (approval no. Eki491), and informed consent was obtained from all patients via an opt-out procedure on the website (http://setouchi-bp.com/ippan/ntouroku.html) and by announcing this study via a poster in the outpatient clinic. All medical procedures were carried out in accord with relevant guidelines and regulations. The study-related procedures were conducted in accord with the principles described in the Declaration of Helsinki.

Study endpoints. The primary study endpoint was the patients' RFS, which was defined as the duration from a patient's surgery until the time of local and/or regional recurrence and/or distant metastasis of breast cancer or death from any cause [21]. Local recurrence was defined as tumor recurrence involving the ipsilateral chest wall, skin, subcutaneous tissue, and/or pectoralis muscle. Regional recurrence was defined as recurrence involving the ipsilateral axillary, supraclavicular, internal mammary, and/or infraclavicular lymph nodes. Distant metastasis involved metastatic breast cancer that had spread to other parts of the body. The secondary study endpoints were as follows: (*i*) the patients' OS, which was defined as the time from surgery to follow-up or death; and (*ii*) the time to the initiation of adjuvant chemotherapy, which was defined as the duration from surgery to the initiation of adjuvant chemotherapy. If any events occurred during follow-up, the case was censored.

Statistical analysis. Patient characteristics, prognostic factors, and the time to the initiation of adjuvant chemotherapy were compared among the three groups. For the evaluation of differences between quantitative variables, a one-way analysis of variance (ANOVA) was used to compare the three groups. The Kruskal–Wallis test was used when normality of the population distribution could not be assumed. The Shapiro–Wilk test was used to examine normality. Categorical variables were investigated using Pearson's χ^2 test. Univariate and multivariate Cox's proportional hazards models were used to evaluate independent prognostic factors for RFS and OS. We evaluated the surgical procedures (IBR, mastectomy, BCS), patient age (< 50 years, ≥ 50 years old), ER (positive, negative), PgR (positive, negative), HER2 (positive, negative), lymphovascular invasion (positive, negative), nuclear grade (1, 2, 3), tumor size (ductal carcinoma in situ [DCIS], 0-2 cm, > 2 cm), and lymph node metastasis (positive, negative). Hazard ratios and their 95% confidence intervals (95%CIs) were calculated using Cox's proportional hazard model. Statistical calculations were performed using SPSS Statistics ver. 24.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics. During the study period, 773 patients were enrolled from the database. A total of 159 patients were excluded, and 614 patients participated in the study (Fig. 1). Of these 614 patients, 125 patients underwent IBR, 128 patients underwent mastectomy, and 361 patients underwent BCS. In the IBR

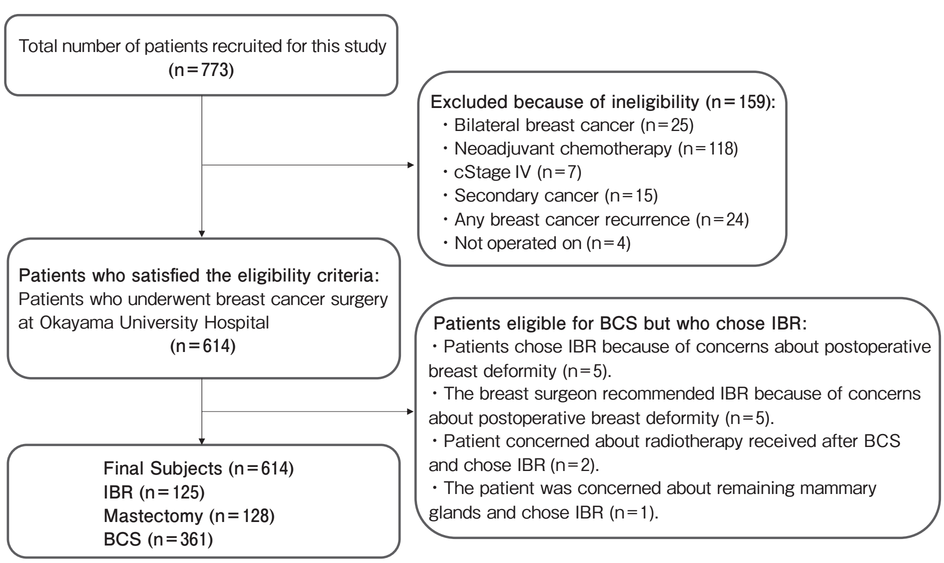

Fig. 1 Study flowchart. In this study, 773 patients were registered, and 614 were included in the analysis. There were overlapping reasons for exclusions.

group, 79 patients underwent nipple-sparing mastectomy (63.2%), while 35 patients underwent skin-sparing mastectomy (28.0%). The median follow-up duration of all 614 patients was 79.0 ± 31.9 months (interquartile range: 62-101 months).

The patient characteristics are summarized in Table 1. The median ages were 46.0 years for IBR, 67.0 years for mastectomy, and 59.0 years for BCS. The patients who had undergone IBR were younger than those in the other groups, and the proportion of premenopausal patients was highest in the IBR group. Larger tumors were more common in the IBR and mastectomy groups than in the BCS group. The proportion of histological axillary lymph node metastases was 30.4% for IBR, 34.4% for mastectomy, and 16.6% for BCS, *i.e.*, higher in the IBR and mastectomy groups than in the BCS group. Advanced disease was more common in the IBR and mastectomy groups compared to the BCS group. Lymphovascular invasion was most common in the mastectomy group. The proportions of adjuvant chemotherapy were 35.2% for IBR, 25.8% for mastectomy, and 22.7% for BCS, *i.e.*, highest in the IBR group. Missing data were similar across the surgical types and were low for most of the demographic information.

Survival outcomes. The univariate Cox's regression analysis of factors associated with RFS indicated that BCS (hazard ratio [HR]: 0.40, 95%CI: 0.210-0.777) was associated with better RFS, while positive lymphovascular invasion (HR 2.54, 95%CI: 1.443-4.451), nuclear grade 3 (HR 3.87, 95%CI: 1.819-8.243), tumor size > 2 cm (HR 3.17, 95%CI: 1.278-7.856), and lymph node metastasis positivity (HR 2.55, 95%CI: 1.450-4.478) were associated with worse RFS. The multivariate Cox's regression analysis revealed that BCS (HR 0.33, 95%CI: 0.144-0.763) was associated with better RFS, and nuclear grade 3 (HR 2.88, 95%CI: 1.174-7.060) was associated with worse RFS (Table 2).

The univariate Cox's regression analysis of factors associated with OS revealed that age < 50 years (HR 0.16, 95%CI: 0.057-0.444) was associated with better OS, while mastectomy alone (HR 5.08, 95%CI: 1.924-13.426), the presence of lymphovascular invasion (HR 2.81, 95%CI: 1.573-5.033), nuclear grade 3 (HR 3.71, 95%CI: 1.663-8.253), tumor size 0-2 cm (HR 4.32, 95%CI: 1.024-18.190), tumor size > 2 cm (HR 9.52, 95%CI: 2.231-40.600), and lymph node positivity (HR 3.06, 95%CI: 1.671-5.609) were associated with worse OS. The multivariate results indicated that age < 50 years (HR 0.24, 95%CI: 0.078-0.734) and HER2-positive status (HR 0.26, 95%CI: 0.075-0.922) were associated with better OS, and nuclear grade 3 (HR 3.46, 95%CI: 1.191-10.054) was associated with worse OS (Table 3).

Table 4 provides the details of the RFS events. Local recurrences were diagnosed in ten patients who had undergone IBR (8.0%), two who had undergone mastectomy (1.6%), and 11 who had undergone BCS (3.0%). The proportion of local recurrence was thus higher in the IBR group compare to the mastectomy and BCS groups (Table 5).

The details of the local recurrences in the IBR group were as follows: three patients were pStage0, five patients were pStage1, and two patients were pStage2. No patient received postoperative radiation therapy. The median time to the detection of local recurrence was 54.5 months. Four of the 10 patients had local recurrence for > 60 months. All local recurrences were observed in residual skin. Five recurrences were detected via self-examination, and five were detected during a clinical examination. Regional recurrence, distant metastasis, and death from any cause each showed similar incidence proportions among the IBR, mastectomy, and BCS groups.

Treatment-related outcomes. The data of the lengths of time from surgery to the initiation of adjuvant chemotherapy are presented in Table 6. The times were 39.1 ± 12.4 days for the IBR group, 39.1 ± 12.6 days for the mastectomy group, and 49.7 ± 24.7 days for the BCS group. The time to the initiation of adjuvant chemotherapy was thus longest in the BCS group. One patient each in the IBR and mastectomy groups and 10 patients in the BCS group experienced a delay in the initiation of adjuvant chemotherapy beyond 12 weeks postsurgery. These delays occurred for the following reasons: The patient in the IBR group underwent bladder cancer surgery before adjuvant chemotherapy, and the chemotherapy administration schedule for the mastectomy-group patient changed because of her poor health. The delays were 1 and 2 days, respectively. One patient in the BCS group underwent additional surgery because of positive margins; for the other nine patients, radiation therapy was preceded by adjuvant chemotherapy.

Table 1 Demographic information for all patients by surgical type

Characteristics	Number of patients (%)			*P*-value
	IBR[a] (n = 125)	Mastectomy (n = 128)	BCS[b] (n = 361)	
Age at diagnosis, years				<0.001*
Median	46	67	59	
Range	26 to 67	27–94	22–97	
Interquartile range	41.5 to 50.5	54.50 to 67.00	48.00 to 67.00	
Missing	0	0	0	
Body mass index, kg/m^2				0.05*
Median	21.6	22.4	22.2	
Range	18 to 30	15 to 36	15 to 42	
Interquartile range	20.0 to 23.4	20.0 to 25.7	20.3 to 24.8	
Missing	0	0	0	
Pre-menopause				
No	30 (24.0)	100 (78.1)	232 (64.3)	<0.001**
Yes	93 (74.4)	26 (20.3)	126 (34.9)	
Missing	2 (1.6)	2 (1.6)	3 (0.8)	
Tumor size (cm)				<0.001**
0< to ≤2	89 (71.2)	84 (65.6)	304 (84.2)	
>2	36 (28.8)	44 (34.4)	54 (15.0)	
Missing	0	0	3 (0.8)	
Positive lymph node status				<0.001**
No	87 (69.6)	84 (65.6)	287 (79.5)	
Yes	38 (30.4)	44 (34.4)	60 (16.6)	
Missing	0	0	14 (3.9)	
Pathological tumor stage				<0.001**
0	35 (28.0)	19 (14.8)	70 (19.4)	
1	42 (33.6)	48 (37.5)	189 (52.4)	
2	34 (27.2)	40 (31.3)	86 (23.8)	
3	14 (11.2)	21 (16.4)	13 (3.6)	
Missing	0	0	3 (0.8)	
Adjuvant chemotherapy				0.021**
No	80 (64.0)	95 (74.2)	278 (77.0)	
Yes	44 (35.2)	33 (25.8)	82 (22.7)	
Missing	1 (0.8)	0	1 (0.3)	
Lymphovascular invasion				0.024**
No	75 (60.0)	69 (53.9)	238 (65.9)	
Yes	48 (38.4)	59 (46.1)	116 (32.1)	
Missing	2 (1.6)	0	7 (1.9)	
Nuclear grade				0.088**
1	29 (23.2)	36 (28.1)	112 (31.0)	
2	29 (23.2)	30 (23.4)	91 (25.2)	
3	29 (23.2)	39 (30.5)	75 (20.8)	
Missing				
Estrogen receptor status				0.337**
Negative	22 (17.6)	30 (23.4)	64 (17.7)	
Positive	101 (80.8)	97 (75.8)	295 (81.7)	
Missing	2 (1.6)	1 (0.8)	2 (0.6)	
Human epidermal growth factor receptor 2 status				0.128**
Negative	99 (79.2)	98 (76.6)	299 (82.8)	
Positive	16 (12.8)	19 (14.8)	82 (22.7)	
Missing	10 (8.0)	11 (8.6)	30 (8.3)	
Median follow-up time, months	84	79	75	

[a]IBR, immediate breast reconstruction; [b]BCS, breast conservative surgery.

Table 2 Univariate and multivariate Cox's proportional hazard regression analyses of factors associated with recurrence-free survival

Variables	Univariate			Multivariate		
	HR[a]	95% CI[b]	*P*-value	HR	95%CI	*P*-value
Surgical methods						
IBR[c]	Ref.[d]			Ref.		
BCS[e]	0.40	0.210–0.777	0.007	0.33	0.144–0.763	0.009
Mastectomy	1.02	0.510–2.053	0.95	0.92	0.407–2.080	0.841
Age, years						
≥50	Ref.			Ref.		
<50	1.05	0.592–1.847	0.878	0.84	0.402–1.743	0.635
Estrogen receptor status						
Negative	Ref.			Ref.		
Positive	0.67	0.359–1.266	0.22	1.15	0.426–3.067	0.790
Progesterone receptor status						
Negative	Ref.			Ref.		
Positive	0.63	0.352–1.110	0.109	0.73	0.298–1.790	0.492
Human epidermal growth factor receptor 2 status						
Negative	Ref.			Ref.		
Positive	1.73	0.838–3.571	0.139	0.92	0.390–2.176	0.851
Lymphovascular invasion						
Negative	Ref.			Ref.		
Positive	2.54	1.443–4.451	0.001	1.28	0.566–2.914	0.998
Nuclear grade						
1	Ref.			Ref.		
2	1.18	0.468–2.973	0.726	1.00	0.368–2.707	0.998
3	3.87	1.819–8.243	<0.001	2.88	1.174–7.060	0.021
Tumor size (cm)						
DCIS[f]	Ref.			Ref.		
>0 to ≤2	1.32	0.538–3.221	0.547	NA[g]	–	0.997
>2	3.17	1.278–7.856	0.013	NA	–	0.997
Lymph node status						
Negative	Ref.			Ref.		
Positive	2.55	1.450–4.478	0.001	1.39	0.671–2.877	0.376

[a]HR, hazard ratio; [b]CI, confidence interval; [c]IBR, immediate breast reconstruction; [d]Ref, reference category; [e]BCS, breast conservative surgery; [f]DCIS, ductal carcinoma in situ; [g]NA, not assessed.

Discussion

We investigated the oncological safety of IBR by comparing three surgical techniques: IBR, mastectomy, and BCS. The results of our analyses demonstrated that IBR had an effect on RFS when compared with BCS.

In an observational study, Siotos *et al.* compared the prognoses among 1,517 patients who underwent IBR or mastectomy, and they observed no significant differences in the patients' recurrence or OS [22]. The following three systematic reviews compared prognoses between IBR and mastectomy. Mgieni *et al.* reviewed eight cohort studies and two matched cohort studies; for the eight cohort studies, they analyzed the data of 2,917 patients who underwent mastectomy and 793 patients who underwent IBR. The two matched cohort studies included 358 patients. They investigated patients with invasive breast cancer, comparing IBR and mastectomy, and concluded that there were no significant differences in the frequency of local recurrence or distant metastasis between IBR and mastectomy [23]. Zhang *et al.* reviewed 31 studies encompassing 139,894 patients and concluded that compared with mastectomy, IBR did not affect OS, disease-free survival, or local recurrence [24]. Yang *et al.* reviewed 14 studies encompassing 3,641 patients who underwent breast reconstruction and 9,462 controls. Of these studies,

Table 3 Univariate and multivariate Cox's proportional hazard regression analyses of factors associated with overall survival

Variables	Univariate			Multivariate		
	HR[a]	95% CI[b]	*P*-value	HR	95% CI	*P*-value
Surgical methods						
IBR[c]	Ref.[d]			Ref.		
BCS[e]	1.65	0.626–4.367	0.310	0.79	0.263–2.378	0.676
Mastectomy	5.08	1.924–13.426	0.001	2.29	0.793–6.603	0.126
Age, years						
≥50	Ref.			Ref.		
<50	0.16	0.057–0.444	<0.001	0.24	0.078–0.734	0.013
Estrogen receptor status						
Negative	Ref.			Ref.		
Positive	0.72	0.374–1.375	0.317	0.59	0.191–1.847	0.368
Progesterone receptor status						
Negative	Ref.			Ref.		
Positive	0.72	0.394–1.300	0.272	1.14	0.421–3.104	0.368
Human epidermal growth factor receptor 2 status						
Negative	Ref.			Ref.		
Positive	0.85	0.336–2.142	0.728	0.26	0.075–0.922	0.037
Lymphovascular invasion						
Negative	Ref.			Ref.		
Positive	2.81	1.573–5.033	<0.001	1.53	0.637–3.657	0.343
Nuclear grade						
1	Ref.			Ref.		
2	2.07	0.867–4.926	0.102	2.25	0.766–6.620	0.140
3	3.71	1.663–8.253	0.001	3.46	1.191–10.054	0.023
Tumor size, cm						
DCIS[f]	Ref.			Ref.		
>0 to ≤2	4.32	1.024–18.190	0.046	NA[g]	–	0.997
>2	9.52	2.231–40.600	0.002	NA	–	0.997
Lymph node status						
Negative	Ref.			Ref.		
Positive	3.06	1.671–5.609	<0.001	1.51	0.688–3.300	0.306

[a]HR, hazard ratio; [b]CI, indicates confidence interval; [c]IBR, immediate breast reconstruction; [d]Ref, reference category; [e]BCS, breast conservative surgery; [f]DCIS, ductal carcinoma in situ; [g]NA, not assessed.

Table 4 Details of the relapse-free survival events

	Number of patients (%)		
First event	IBR[a] n=125	Mastectomy n=128	BCS[b] n=361
Local recurrence only	7 (5.6)	1 (0.8)	11 (3.0)
Regional recurrence only	1 (0.8)	2 (1.6)	1 (0.3)
Distant metastasis only	5 (4.0)	11 (8.6)	8 (2.2)
Local recurrence and regional recurrence	0 (0)	0 (0)	0(0)
Local recurrence and distant metastasis	2 (1.6)	0 (0)	0 (0)
Local recurrence, regional recurrence, and distant metastasis	1 (0.8)	1 (0.8)	0 (0)
Death from any cause	0 (0)	14 (10.9)	15 (4.2)
Total	16	15	20

[a]IBR, immediate breast reconstruction; [b]BCS, breast conservative surgery.

Table 5 Comparison of the proportion of local recurrence among surgical procedures

	Number of patients (%)			
First event	IBR[a] n = 125	Mastectomy n = 128	BCS[b] n = 362	*P*-value
Local recurrence	10 (8.0)	2 (1.6)	11 (3.0)	0.02*

*Pearson χ^2 test
[a]IBR, immediate breast reconstruction; [b]BCS, breast conservative surgery.

Table 6 Timing until the initiation of adjuvant chemotherapy

	IBR[a] (n = 44)	Mastectomy (n = 29)	BCS[b] (n = 80)	*P*-value
Interval from surgery to chemotherapy (d)	39.1 ± 13.4	39.1 ± 12.6	49.7 ± 24.7	0.04*
More than 84 days (%)	1 (2.3)	1 (3.45)	10 (12.5)	

*The Kruskal-Wallis test was used for comparisons among the three groups.
[a]IBR, immediate breast reconstruction; [b]BCS, breast conservative surgery.

two enrolled both patients with BCS and nipple-sparing mastectomy as controls. Yang *et al*. concluded that the overall recurrence, DFS, and OS were not significantly different between the reconstruction and control groups [25]. The authors of all three reviews concluded that IBR does not affect oncological safety compared with mastectomy.

Our present analyses revealed that the patients who underwent IBR had more advanced breast cancer and that many patients who underwent breast reconstruction received adjuvant chemotherapy. This result means that, at our institution, IBR can be performed even in advanced cases if the patient wishes.

Regarding the primary study endpoint, the multivariate results indicated that there were no significant differences in RFS between the IBR and mastectomy groups, in agreement with previous findings. However, compared to IBR, BCS was more closely associated with better RFS. The proportion of local recurrence was highest among the IBR patients, and all of them did not receive PMRT.

Lim *et al*. investigated the oncological safety of IBR for locally advanced breast cancer and, as we also observed herein, they noted that all the patients with local recurrence did not receive PMRT [13]. These results support the conventional concerns that when a patient undergoes IBR, the occult malignant cells in the residual skin contribute to local recurrence. There is also a tendency for inadequate control of local recurrence in patients who do not receive PMRT. In contrast, the patients who underwent mastectomy had excess skin removed, and all of the patients in the BCS group were scheduled to receive PMRT. This explains why occult malignant cells in both groups exhibited poor survival [26,27].

Among the present study's patients with local recurrence, eight patients survived after undergoing local resection or additional chemoradiation whereas two patients died, including one patient who had a high-risk malignancy (triple-negative, Ki-67 > 50%). She was treated with adjuvant chemotherapy; however, she was diagnosed with local recurrence and pulmonary metastasis at 2 years postoperatively. The other patient had to change her chemotherapy regimen due to complications, and chemotherapy was later suspended. Treatment with hormone therapy alone was continued. Local recurrence was observed in patients with infra-clavicular and internal mammary lymph node metastasis and liver metastasis at 4 years postoperatively. We concluded that neither death was related to the patient's breast reconstruction.

All local recurrences in the IBR group were identified on the skin side. Our results indicate that detecting local recurrence is not difficult and that regular self- or clinical examination is crucial. Lucy *et al*. investigated the proportion of local recurrence after nipple-sparing mastectomy and calculated it based on three follow-up intervals: < 3, 3-5, and > 5 years with proportions of 5.4%, 1.4%, and 11.4%, respectively [8]. This implies that some patients who complete 5 years of hormone therapy may relapse after treatment. In the present study, the median time to the detection of local recurrence in the reconstruction group was 54.5 months, with approx. 40% of cases occurring at >5 years postoperatively. This suggests that long-term follow-up is necessary, especially for patients who have undergone breast reconstruction.

Reddy *et al*. noted that the proportion of local recurrence after IBR has been reported to be 1-24% in previous studies, concluding that this large range is attributable to differences in the breast cancer stage at presentation and differences in follow-up periods [7]. Our present analyses revealed that the proportion of local recurrence was highest in the patients who underwent IBR. This may be related to the relatively long follow-up period in our study.

Regarding the time to the initiation of adjuvant chemotherapy, although, several studies have reported a higher incidence of wound complications for IBR than for mastectomy, many studies have concluded that time from surgery to chemotherapy induction does not affect the cancer treatment outcome in patients undergoing IBR [28-31]. Among our present IBR, mastectomy, and BCS groups, there were differences in the length of time to the initiation of adjuvant chemotherapy; this is because some patients in the BCS group underwent prior PMRT. The time to the initiation of adjuvant chemotherapy in the IBR and mastectomy groups was similar. The chemotherapy of one patient who underwent IBR was delayed for >12 weeks, but the delay was not related to procedural complications. Although we did not investigate complications directly, our results revealed that IBR did not delay the initiation of adjuvant chemotherapy. The multivariate results concerning the patients' overall survival also demonstrated that IBR was not a predictor of survival.

The limitations of this study are the relatively small number of patients, the single institution as the source of patients, and the observational study type, which may involve selection bias, follow-up bias, and the presence of confounding factors that were not understood. Randomized trials are necessary for high-quality research; however, studies comparing IBR and non-IBR are difficult for ethical reasons, and observational studies such as the present study are thus relevant. In addition, there have been no published comparisons of IBR, mastectomy alone, and BCS groups. We believe that our study, which included such comparisons, is therefore meaningful. Because our reconstruction group tended to be younger and included cases of more advanced cancer, a matched-pair analysis would be appropriate to match the patient backgrounds. However, due to the relatively small number of patients, such matching was difficult.

Although there were more cases of progression in the IBR group, it is worth considering that local recurrence in this group was more common in the patients with pStage0 or pStage1 disease. None of these patients were eligible for PMRT, and the patient with recurrence at pStage2 did not undergo PMRT. This shows the importance of PMRT in patients who undergo breast reconstruction.

In conclusion, the results of our analyses indicate that immediate breast reconstruction was associated with lower recurrence-free survival compared to breast conservative surgery. In particular, the proportion of local recurrence was higher among the patients who had not received postoperative radiation therapy. These results indicate that it is important to make careful decisions about the indications for reconstruction in patients who are not scheduled for postoperative radiation therapy. The risk of local recurrence should therefore be explained prior to surgery, and long-term follow-up is required postoperatively. Multi-institution trials are necessary to provide safer and more reliable IBR.

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