Oncologic Outcomes of Immediate Breast Reconstruction in Young Women with Breast Cancer Receiving Neoadjuvant Chemotherapy

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Abstract

Background: Oncologic safety of postmastectomy breast reconstruction in young women with breast cancer is not well-defined, especially in the setting of neoadjuvant chemotherapy (NACT). We retrospectively compared the oncologic outcomes following nipple-sparing (NSM)/skin-sparing mastectomy (SSM) with immediate breast reconstruction (IBR) and conventional mastectomy (CM) alone in young breast cancer patients after NACT.

Methods: A total of 1266 women with primary breast cancer who underwent NACT followed by total mastectomy with or without IBR were reviewed. Of these, only young patients (age ≤40 years at diagnosis) were included in the outcome analysis (n=375). After propensity score-matching by clinical T and N stage, molecular subtype, response to NACT, and adjuvant radiotherapy status, 228 patients were 1:1 matched, comprising balanced IBR group (with NSM/SSM) and CM-alone group.

Results: The 5-year locoregional recurrence-free, disease-free, distant metastasis (DM)-free, and breast cancer-specific survival (BCSS) rates for the entire cohort of young patients were 83.4%, 65.3%, 71.7%, and 85.4%, respectively. Locoregional recurrence rates between the matched groups were similar (14% vs. 15.8%; $P = 0.710$); however, IBR group had significantly lower DM rate (27.2% vs. 40.4%; $P = 0.036$) and breast cancer mortality (14.9% vs. 27.2%; $P = 0.023$) than CM-alone group. IBR group showed significantly improved 5-year DM-free survival (74.1% vs. 62.6%; $P = 0.043$) and BCSS (89.1% vs. 77.6%; $P = 0.048$) rates than CM-alone group.

Conclusions: Our results indicated that IBR with NSM/SSM does not negatively affect long-term oncologic outcomes compared to CM alone in young women with breast cancer receiving NACT.

Introduction

The incidence of breast cancer is increasing worldwide [1]. According to the data from GLOBOCAN, approximately 2.2 million women have been newly diagnosed with breast cancer in 2020, accounting for 24.5% of all female malignancies [1]. The proportion of young patients, which generally refers to patients under 40 years of age, among all breast cancer patients is not large (4–7% in Western countries [2, 3] and 10–14% in Asian countries [4, 5]); however, breast cancer is still the most prevalent cancer with the highest mortality among young women [6]. Historically, young age at diagnosis itself is a prognostic factor associated with adverse breast cancer outcomes [7]. Compared to the older counterparts, younger women with breast cancer are more likely to present with more aggressive tumor characteristics such as higher tumor grade, larger tumor size, higher incidence of nodal involvement, and more lympho-vascular invasion (LVI) [8–10]. In addition, because of the higher likelihood of having hormone receptor-negative tumors [8–10], young patients are more likely to benefit from neoadjuvant chemotherapy (NACT).

In addition to the concerns regarding cancer diagnosis, young women with breast cancer may also be distressed at facing the potential oncologic treatment-associated damage to their body image [11]. Although breast-conserving surgery may have less negative impact on the patient's postoperative body

image and quality of life than other surgical procedures [12] and NACT can increase the rate of breast conservation [13], there is still a large proportion of patients who will undergo total mastectomy after receiving NACT [14, 15]. Nipple-sparing (NSM) or skin-sparing mastectomy (SSM), combined with immediate breast reconstruction (IBR), can be an important alternative for young women with breast cancer because this procedure can provide superior aesthetic results and improved patients' quality of life compared with conventional mastectomy (CM) alone [16–18]. Several studies have documented increasing trends in NSM/SSM and breast reconstruction in younger patients [19–21]. However, the oncologic safety of this procedure is not well-defined in young women with breast cancer, especially in the setting of NACT. To our knowledge, to date, no study has compared the oncologic outcomes of IBR and CM alone in young breast cancer patients receiving NACT. Therefore, in this study, we sought to compare the oncologic outcomes following IBR and CM alone in young patients with breast cancer who were treated with NACT.

Patients And Methods

The records from a prospectively maintained database were reviewed for patients who had undergone NACT followed by total mastectomy, with or without immediate breast reconstruction, between January 1, 2010, and November 30, 2016 at Asan Medical Center (Seoul, Korea) after receiving institutional review board approval. We excluded patients with inflammatory breast cancer or pathological T4 disease, synchronous distant metastasis (DM), or recurrent disease. Only patients aged ≤ 40 years at the time of diagnosis were included in the outcome analysis.

All patients included in this study received NACT after the diagnosis of breast cancer. The NACT regimens were selected at the discretion of the treating oncologist. All patients who underwent IBR were combined with NSM or SSM. NSM/SSM was performed according to the indications of conventional mastectomy, as long as there was no evidence for tumor involvement in the breast skin/nipple-areolar complex clinically and on imaging. In NSM cases, retroareolar frozen-section biopsy specimens were collected and examined intraoperatively. The nipple–areola complex was preserved if the shape, color, and palpated features of the nipple were normal, and if the nipple margin was confirmed to be tumor-free on frozen-section biopsy. In cases in which the retroareolar tissue was positive for malignancy in the frozen section or permanent biopsy, the nipple with or without the areola was removed, and the surgical procedure was converted to SSM. In our entire cohort, no patient was converted to CM due to failure of the NSM/SSM procedure.

Postoperatively, the patients were regularly followed up every 3–6 months for the first 5 years and annually thereafter. Recurrences and metastases were assessed by clinical examination and chest radiography during every follow-up visit. Abnormal clinical findings have been evaluated through further studies, including ultrasonography, computed tomography of the chest, and bone scanning. In patients suspected of having a local or regional recurrence, fine needle aspiration, core-needle, or excisional biopsy was performed for pathological confirmation. In patients diagnosed with locoregional recurrence (LRR), we generally performed positron emission tomography (PET)-computed tomography (CT) to rule out

DMs. However, in some cases, CT and/or bone scan was performed instead of PET-CT based on the judgment of the treating physician. Identification of lesions with clear evidence of distant metastasis on imaging was considered recurrence without pathological examination. LRRs were classified as biopsy-proven local recurrences in the ipsilateral nipple-areola complex, skin/subcutaneous layer, or chest wall and as regional recurrences defined as carcinoma metastases involving the ipsilateral axillary, supraclavicular, or internal mammary lymph node. Any other site of recurrence was considered to be DM.

To reduce the effects of selection bias on the type of surgery and confounding factors on the comparison of the oncologic outcomes between the IBR and CM-alone groups, we used propensity-score matching to create well-balanced groups. We included the following baseline covariates for matching: clinical T stage, clinical N stage, molecular subtype, pathological complete response (pCR) status, and adjuvant radiotherapy status. Propensity scores were calculated for each patient using a multivariate logistic regression model, and patients were matched 1:1 into IBR with NSM/SSM and CM-alone groups using caliper restriction to the nearest neighbor without replacement. Tumor stage was determined according to the 8th edition of the American Joint Committee on Cancer Staging Manual [22]. A pCR was defined as no evidence of invasive cancer in the breast and axillary lymph node.

Statistical Analyses

The endpoints of interest were locoregional recurrence-free survival (LRFS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and breast cancer-specific survival (BCSS). Patients with initial DM were excluded from the LRR group. In cases of concurrent LRR or DM, each recurrence was counted simultaneously as an event. Follow-up was calculated from the date of diagnosis. The LRFS, DFS, DMFS, and BCSS rates were calculated using the Kaplan–Meier method and compared using log-rank tests. The chi-squared or Fisher's exact test was used for intergroup comparisons. The clinicopathological factors associated with DMFS were analyzed using the univariate and multivariate Cox proportional hazards regression model. All statistical analyses were performed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Two-tailed *P*-values < 0.05 were considered statistically significant. Data analysis was performed from August 1, 2020, to February 26, 2021.

Results

Baseline Characteristics for the Entire Cohort

A total of 1395 patients were treated with NACT and mastectomy during the study period. Among these, patients with inflammatory breast cancer or pathological T4 disease, synchronous DM, or recurrent disease were excluded (n = 129). Accordingly, 1266 patients were included in the analysis. Among these, 375 patients (29.6%) were aged ≤ 40 years, and 891 patients (70.4%) were aged > 40 years. IBR was performed in 64.3% of patients aged ≤ 40 years and in 32% of those aged > 40 years (*P* < 0.001). The baseline characteristics for the 375 patients aged ≤ 40 years are shown in Table 1. The study cohort

comprised 241 patients who underwent IBR with NSM/SSM and 134 patients who underwent CM alone. Patients in the IBR group were more likely to be at earlier clinical and pathological stages, to have hormone-positive disease, and to receive adjuvant radiotherapy than those in the CM-alone group. However, the pCR status did not differ significantly between the groups.

Table 1
Baseline characteristic for the entire cohort before matching

Variables		Total, n = 375	%	IBR, n = 241	%	CM, n = 134	%	*P*
Age, Median (range), years		36 (23–40)		36 (23–40)		37 (25–40)		
Clinical T stage	cT1	18	4.8	17	7.1	1	0.7	< 0.001
	cT2	185	49.3	130	53.9	55	41.0	
	cT3-4	172	45.9	94	39.0	78	58.2	
Clinical N stage	cN0	98	26.1	76	31.5	22	16.4	< 0.001
	cN1	176	46.9	121	50.2	55	41.0	
	cN2-3	101	26.9	44	18.3	57	42.5	
Molecular subtype	HR+/HER2-	171	45.6	122	50.6	49	36.6	0.001
	HR+/HER2+	93	24.8	64	26.6	29	21.6	
	HR-/HER2+	46	12.3	26	10.8	20	14.9	
	TNBC	65	17.3	29	12.0	36	26.9	
pCR	Yes	43	11.5	29	12.0	14	10.4	0.644
	No	332	88.5	212	88.0	120	89.6	
Pathological T stage	ypT0/Tis	51	13.6	32	13.3	19	14.2	0.236
	ypT1	127	33.9	89	36.9	38	28.4	
	ypT2-3	197	52.5	120	49.8	77	57.5	
Pathological N stage	ypN0	149	39.7	102	42.3	47	35.1	0.146
	ypN1	140	37.3	91	37.8	49	36.6	
	ypN2-3	86	22.9	48	19.9	38	28.4	
Histotype	IDC	329	87.7	214	88.8	115	85.8	0.461
	ILC	7	1.9	4	1.7	3	2.2	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer. *Unknown, n = 37

Variables		Total, n = 375	%	IBR, n = 241	%	CM, n = 134	%	*P*
	Mixed	22	5.9	15	6.2	7	5.2	
	Others	17	4.5	8	3.3	9	6.7	
Histologic grade	1,2	245	65.3	162	67.2	83	61.9	0.303
	3	130	34.7	79	32.8	51	38.1	
LVI	Yes	162	43.2	107	44.4	55	41.0	0.53
	No	213	56.8	134	55.6	79	59.0	
Post-NACT Ki67 *	< 10%	154	45.6	103	48.1	51	41.1	0.213
	≥ 10%	184	54.4	111	51.9	73	58.9	
Adjuvant radiotherapy	Yes	237	63.2	130	53.9	107	79.9	< 0.001
	No	138	36.8	111	46.1	27	20.1	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer. *Unknown, n = 37

Oncologic Outcomes of the Entire Cohort

The median follow-up duration for the entire cohort (n = 375) was 72 (range, 9–138) months. During this period, recurrences were observed in 137 patients (36.5%). DM was observed in 112 patients (29.9%); LRR as the first event was observed in 60 patients (16%). Breast cancer-associated death occurred in 70 patients (18.7%). The median time to DM and LRR as the first event was 30 months (range, 6–99 months) and 24 months (range, 5–76 months), respectively. The 5-year LRFS, DFS, DMFS, and BCSS rates were 83.4%, 65.3%, 71.7%, and 85.4%, respectively. A total of 43 patients (11.5%) achieved pCR. Among these, 6 patients (14%) showed recurrence, including 3 patients (7.0%) with DM, 2 patients (4.7%) with LRR, and 1 patient (2.3%) with concurrent LRR and DM. The following factors were significantly associated with reduced DMFS in the univariate analysis: clinical N stage, pathological T stage, pathological nodal status, triple-negative subtype, pCR status, LVI, and post-NACT Ki67 index (Table 2). Of these, clinical N2–3 stage, pathological T2–3 stage, pathological nodal positivity, triple-negative subtype, and post-NACT Ki67 ≥ 10% were independently associated with reduced DMFS in the multivariate analysis (Table 2).

Table 2
Univariate and multivariate analyses for the risk factors associated with reduced distant metastasis-free survival

		Univariate analysis		Multivariate analysis	
Variables		HR (95% CI)	*P*	HR (95% CI)	*P*
Clinical T stage	cT1–2	Ref	0.165		
	cT3–4	1.012 (0.995–1.029)			
Clinical N stage	cN0–1	Ref	< 0.001	Ref	< 0.001
	cN2–3	2.523 (1.734–3.671)		1.043 (1.025–1.061)	
Pathological T stage	ypT0–1	Ref	< 0.001	Ref	0.005
	ypT2–3	1.037 (1.019–1.056)		1.027 (1.008–1.047)	
Pathological nodal status	ypN-	Ref	< 0.001	Ref	0.005
	ypN+	2.618 (1.678–4.086)		1.989 (1.225–3.229)	
Molecular subtype	Non-TNBC	Ref	< 0.001	Ref	< 0.001
	TNBC	2.584 (1.706–3.914)		3.137 (1.996–4.931)	
pCR	Yes	Ref	0.006	Ref	0.333
	No	4.084 (1.505–11.080)		2.088 (0.470–9.271)	
Histologic grade	1, 2	Ref	0.149		
	3	1.323 (0.905–1.933)			
LVI	No	Ref	< 0.001	Ref	0.313
	Yes	1.977 (1.359–2.874)		1.232 (0.821–1.848)	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer.

		Univariate analysis		Multivariate analysis	
Post-NACT Ki67	< 10%	Ref	0.009	Ref	0.048
	≥ 10%	1.669 (1.134–2.457)		1.517 (1.005–2.290)	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer.

Patient, Tumor, and Treatment Characteristics for the Matched Groups

After propensity score matching, 228 patients were 1:1 matched into well-balanced IBR (n = 114) and CM-alone (n = 114) groups. Patient and tumor characteristics for the matched groups are shown in Table 3. There were no significant differences between the matched groups in the selected matching variables (i.e., clinical T and N stages, molecular subtype, pCR status, and radiotherapy status) and pathological variables (pathological T and N stage, histotype, histologic grade, LVI, or post-NACT Ki67 status). The treatment characteristics for the matched groups are shown in Table 4. There were no significant differences between the matched groups in NACT regimens, adjuvant radiotherapy, adjuvant hormonal therapy, adjuvant chemotherapy, or targeted therapy for human epidermal growth factor 2-positive (HER2+) disease.

Table 3
Patient and tumor characteristics for the matched groups

Variables		IBR group, n = 114	%	CM group, n = 114	%	*P*
Age, Median (range), years		35 (23–40)		37 (25–40)		
Clinical T stage	cT1	1	0.9	1	0.9	0.867
	cT2	53	46.5	49	43.0	
	cT3–4	60	52.6	64	56.1	
Clinical N stage	cN0	21	18.4	21	18.4	0.839
	cN1	55	48.2	51	44.7	
	cN2–3	38	33.3	42	36.8	
Molecular subtype	HR+/HER2-	47	41.2	49	43.0	0.940
	HR+/HER2+	30	26.3	29	25.4	
	HR-/HER2+	15	13.2	17	14.9	
	TNBC	22	19.3	19	16.7	
pCR	Yes	14	12.3	12	10.5	0.677
	No	100	87.7	102	89.5	
Pathological T stage	ypT0/Tis	16	14.0	16	14.0	0.578
	ypT1	38	33.3	31	27.2	
	ypT2–3	60	52.6	67	58.8	
Pathological N stage	ypN0	40	35.1	41	36.0	0.906
	ypN1	39	34.2	41	36.0	
	ypN2–3	35	30.7	32	28.1	
Histotype	IDC	104	91.2	97	85.1	0.536
	ILC	2	1.8	3	2.6	
	Mixed	4	3.5	6	5.3	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer.

SSM, skin-sparing mastectomy; T, taxane; TEI, tissue expander insertion; TNBC, triple-negative breast cancer. *Unknown, n = 21

Variables		IBR group, n = 114	%	CM group, n = 114	%	*P*
	Others	4	3.5	8	7.0	
Histologic grade	1,2	69	60.5	76	66.7	0.335
	3	45	39.5	38	33.3	
LVI	Yes	55	48.2	46	40.4	0.230
	No	59	51.8	68	59.6	
Post-NACT Ki67 *	< 10%	50	49.5	50	47.2	0.737
	≥ 10%	51	50.5	56	52.8	

CM, conventional mastectomy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; TNBC, triple-negative breast cancer.

SSM, skin-sparing mastectomy; T, taxane; TEI, tissue expander insertion; TNBC, triple-negative breast cancer. *Unknown, n = 21

Table 4
Treatment characteristics for the matched groups

Variables		IBR group, n = 114	%	CM group, n = 114	%	*P*
NACT regimen	AC+/-T	101	88.6	101	88.6	0.328
	T	9	7.9	12	10.5	
	Others	4	3.5	1	0.9	
Mastectomy type	NSM	78	68.4	0	0.0	NA
	SSM	36	31.6	0	0.0	
	CM	0	0.0	114	100.0	
Reconstruction Methods	Autologous flaps	82	71.9	0	0.0	NA
	Implant	32	28.1	0	0.0	
Axillary surgery	SLNB only	48	42.1	34	29.8	0.053
	ALND	66	57.9	80	70.2	
Adjuvant radiotherapy	Yes	91	79.8	87	76.3	0.522
	No	23	20.2	27	23.7	
Adjuvant HT	Yes	78	68.4	79	69.3	0.886
	No	36	31.6	35	30.7	
Adjuvant CTx	Yes	19	16.7	20	17.5	0.860
	No	95	83.3	94	82.5	
Trastuzumab in HER2+	Yes	45	100.0	45	97.8	1.000
	No	0	0.0	1	2.2	

AC, anthracycline; ALND, axillary lymph node dissection; CM, conventional mastectomy; CTx, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HT, hormonal therapy; IBR, immediate breast reconstruction; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MF/MC, multifocality/multicentricity; NA, not applicable; NACT, neoadjuvant chemotherapy; NSM, nipple-sparing mastectomy; pCR, pathological complete response; SLNB, sentinel lymph node biopsy; SSM, skin-sparing mastectomy; T, taxane; TEI, tissue expander insertion; TNBC, triple-negative breast cancer

Oncologic Outcomes of the Matched Groups

After matching, the median follow-up periods were 73 (21–128) and 78 (9–138) months for the IBR and CM-alone groups, respectively. There was no significant difference between the IBR and CM-alone groups

in the rate of LRR as the first event (14% vs. 15.8%; $P = 0.710$); however, the IBR group was associated with significantly lower rates of DM (27.2% vs. 40.4%; $P = 0.036$) and breast cancer-associated death (14.9% vs. 27.2%; $P = 0.023$) than the CM-alone group. There was no significant difference between the IBR and CM-alone groups in the 5-year LRFS (84.5% vs. 83.8%; $P = 0.582$) rate (Fig. 1A); however, the IBR group was associated with significantly improved 5-year DMFS (74.1% vs. 62.6%; $P = 0.043$) rate (Fig. 1C) and BCSS (89.1% vs. 77.6%; $P = 0.048$) rate (Fig. 1D). The IBR group was also associated with an improved 5-year DFS (67% vs. 58.5%; $P = 0.091$) rate with borderline statistical significance compared to the CM-alone group (Fig. 1B).

Discussion

To the best of our knowledge, this is the first report on the comparison of oncologic outcomes following NSM/SSM with IBR versus CM alone, specifically in young women with breast cancer who received NACT. In this study, we observed similar LRR rates between the IBR and CM-alone groups. Moreover, our results showed that NSM/SSM with IBR does not impair the breast cancer outcomes compared with CM alone; on the contrary, we observed that NSM/SSM with IBR was associated with significantly improved 5-year DMFS and BCSS rates compared to CM alone. Furthermore, we found that DM was the most frequently observed recurrence type in the current setting, and tumor features including clinical N2–3 stage, pathological T2–3 stage, pathological nodal positivity, triple-negative subtype, and post-NACT Ki67 ≥ 10% were independently associated with increased risk of DM.

Recently, there has been an increase in the number of breast cancer patients undergoing NSM/SSM with IBR after NACT [19]. Young women with breast cancer were associated with an increased likelihood of undergoing this procedure compared with their older counterparts [19, 23]. In this study, we also observed that postmastectomy IBR was performed more frequently in patients aged ≤ 40 years than in those aged > 40 years in the NACT setting (64.3% vs. 32%; $P < 0.001$). However, younger patients tend to present with more advanced tumor stage, higher histological grade, more LVI, and more aggressive molecular subtype (i.e., HER2-positive/triple negative) [8–10]. Conversely, several studies have reported that the rate of pCR following NACT, which is a surrogate marker for favorable prognosis, was significantly higher among younger patients than in older patients [24, 25]. Accordingly, NACT may be beneficial for young breast cancer patients. However, fear of cancer recurrence can be an imperative reason for not undergoing postmastectomy breast reconstruction in this patient population [26]. There are limited recurrence and survival data available regarding IBR after NACT in young patients that can make it challenging for both surgeons and patients with respect to an informed decision-making process regarding surgical options.

Previous studies have reported improved prognosis in postmastectomy breast reconstruction compared with mastectomy alone for breast cancer [27–31]. In a study based on the data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results registries, Bezuhly et al. demonstrated that IBR is associated with improved BCSS compared to mastectomy alone, particularly among younger women (age < 50 years) with breast cancer [27]. In a retrospective study by Petit et al., the authors performed a matched cohort comparison of 146 patients who underwent implant-based breast

reconstruction versus 146 patients who underwent mastectomy without reconstruction and found that the risks of DM and breast cancer-associated death were significantly lower in the breast reconstruction group than in the control group, while the LRR risk was similar between the matched groups [28]. In another matched cohort study by Eriksen et al., the DM rate and breast cancer mortality were significantly lower in the IBR group than in the mastectomy-alone group after a long-term follow-up [29]. Our findings that IBR is associated with lower rates of DM (27.2% vs. 40.4%) and breast cancer mortality (14.9% vs. 27.2%) compared with CM alone are in agreement with these previously published studies [27–31]; however, our study differs from these previous studies in that our current analyses were exclusively performed in young patients (age ≤ 40 years) receiving NACT, whereas the previous studies involved all age groups and did not compare the outcomes in young patient subgroups or in patients receiving NACT. There are generally substantial differences in baseline characteristics, oncological severity, and adjuvant therapy strategies between the patients undergoing postmastectomy breast reconstruction and those undergoing mastectomy alone. In our study, patients in the IBR group were more likely to be at earlier clinical stages and to have favorable molecular subtype (i.e., hormonal receptor-positive/HER2-negative), but less likely to undergo adjuvant radiotherapy than those in the CM-alone group before matching. After propensity score-matching, these variables were well-balanced between the study groups. In addition, other tumor features including pathological stage, histotype, histologic grade, LVI, and post-NACT Ki67 status, as well as treatment characteristics including NACT regimens, adjuvant hormonal therapy, chemotherapy, and targeted therapy for HER2 + disease, were also identical between the matched groups. Nevertheless, the similarity in the results of our current study and of previously published studies [27–31] in terms of the improved prognosis in the IBR group may be a consequence of selection bias and other hidden confounders, such as socioeconomic status between the comparative groups, even though the main prognostic factors were matched. Another potential prognostic factor that deserves consideration, but was not taken into account in this study, is the stress-related psychosocial impact of the treatments. Successful postmastectomy breast reconstruction is associated with less mental distress and improved patient satisfaction, psychosocial well-being, and quality of life compared with mastectomy alone [32–34]. On the contrary, patients who underwent mastectomy alone may have higher level of postoperative depression and anxiety [32]. Stress-related psychosocial factors may negatively influence the recurrence and survival outcomes of breast cancer [35, 36], and the young patients who have lost their breast due to breast cancer may have higher levels of emotional and psychosocial stress compared to their older counterparts [37].

Although the risk of LRR is generally considered to be an important concern in choosing postmastectomy breast reconstruction or not, there were no significant differences in LRR rate and LRFS between the NSM/SSM with IBR group and CM-alone group in the current study. This result was consistent with those of previous studies investigating the LRR risk following breast reconstruction [28, 29, 38–40]. The most common type of recurrence in the current setting was DM with a rate of 29.9% for the entire cohort. Clinical N stage, pathological T stage, pathological nodal positivity, triple-negative subtype, and post-NACT Ki67 index seemed to be the important risk factors associated with DMFS. The high rate of DM and

poor prognosis in this study population highlights the need for better systemic treatment strategies, especially for young breast cancer patients with such risk factors.

This study is limited by its retrospective design, and the associated selection bias may exist even after matching the key clinical factors. Hidden confounding variables may include, but are not limited to, socioeconomic and psychosocial factors and other clinicopathologic factors. In addition, this study was from a single-institution and involved a relatively small number of patients. Further studies with larger sample size are needed to validate our results. However, in the absence of comparative data, our initial propensity score-matched analysis provides valuable data on the oncologic comparison of NSM/SSM with IBR versus CM alone and may help in the shared decision-making process for the high-risk patient population in the current setting.

Conclusions

Our results indicated that IBR with NSM/SSM did not negatively affect long-term oncologic outcomes compared to CM alone in young women with breast cancer receiving NACT. DM was the most frequently observed recurrence type and clinical N stage, pathological T stage, pathological nodal positivity, triple-negative subtype, and post-NACT Ki67 index were independently associated with reduced DMFS in the current setting.

Declarations

Compliance with ethical standards

Funding: None.

Conflict of interest: None.

Ethical approval: This study was approved by the institutional review board of Asan Medical Center, Seoul, Korea. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Because of the retrospective nature of the study, the requirement for informed consent was waived, and the study was conducted with the exemption of consent under IRB deliberation as it used a platform that offers unidentified clinical information for research purposes.

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Figures

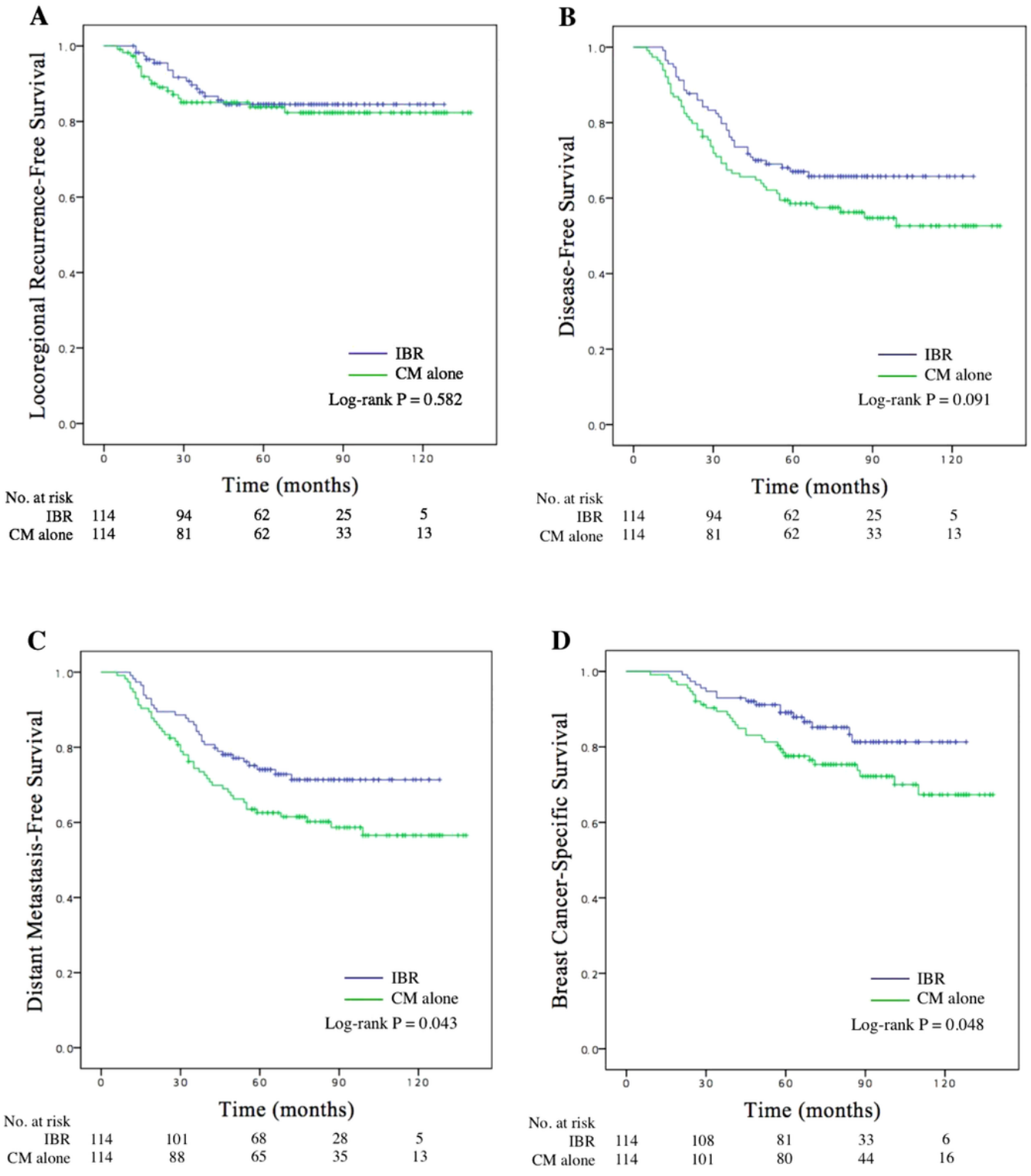

Figure 1

Propensity score-matched Kaplan–Meier survival analyses of locoregional recurrence-free (A), disease-free (B), distant metastasis-free (C), and breast cancer-specific survival (D) between IBR and CM-alone groups. CM, conventional mastectomy; IBR, immediate breast reconstruction