Original Study

Oncologic Safety of Immediate Breast Reconstruction in Breast Cancer Patients Who Underwent Neoadjuvant Chemotherapy: Short-Term Outcomes of a Matched Case–Control Study

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Abstract

We analyzed oncologic outcome by matching variables including age and clinical T and N stage before immediate breast reconstruction (IBR) after neoadjuvant chemotherapy (NACT), response to NACT, and pathologic stage after NACT. IBR after skin-sparing mastectomy or nipple-sparing mastectomy may be a feasible surgical treatment option even in breast cancer patients who underwent NACT.

Introduction: Although the indication for immediate breast reconstruction (IBR) after skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) has been expanded, IBR after neoadjuvant chemotherapy (NACT) is still controversial. We conducted retrospective matched case–control study to analyze oncologic outcomes between patients who underwent TM only and those who underwent IBR after SSM or NSM after NACT. **Patients and Methods:** A retrospective review of breast cancer patients who underwent IBR after SSM or NSM after NACT between 2008 and 2015 at a single center was conducted. These cases were maximally matched by 1:5 to patients who underwent total mastectomy (TM) alone after NACT. Matching variables included age, clinical T and N stage before NACT, response to NACT, and pathologic stage after NACT. Pathologic stage followed the 7th edition of the American Joint Committee on Cancer (AJCC) classification. **Results:** Overall, 31 patients were enrolled onto the IBR after SSM or NSM group (study group) and matched to 85 patients (control group). In the study group, 13 patients (41.9%) underwent NSM and 18 (58.1%) underwent SSM. Median follow-up duration was 29.2 (range, 7-31) and 38.8 (range, 11-85) months for the study and control groups ($P = .012$), respectively, and median age was 37.0 (range, 26-57) and 40.0 (range, 24-56) years ($P = .890$), respectively. Overall survival ($P = .971$), disease-free survival ($P = .520$), distant metastasis-free survival ($P = .795$), and local recurrence-free survival ($P = .628$) did not differ significantly between the 2 groups. **Conclusion:** IBR after SSM or NSM might be a feasible surgical treatment option even in breast cancer patients who underwent NACT.

Clinical Breast Cancer, Vol. ■, No. ■, ■-■ © 2016 Published by Elsevier Inc.

Keywords: Breast cancer, Breast reconstruction, Chemotherapy, Neoadjuvant treatment, Subcutaneous mastectomy

Introduction

Immediate breast reconstruction (IBR) after skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) for patients with breast cancer has been a popular treatment option with similar oncologic outcome to total mastectomy (TM), as well as better patient satisfaction and quality of life.[1-3] With these trends, the

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Submitted: Jul 22, 2016; Revised: Sep 5, 2016; Accepted: Oct 12, 2016

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1526-8209/$ - see frontmatter © 2016 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.clbc.2016.10.009

incidence of IBR has been markedly increased.[4,5] Furthermore, in Korea, the increase in IBR is expected to accelerate because breast reconstruction in patients with breast cancer has been covered by Korean medical insurance since April 2015.

With increased incidence of IBR, the indication of IBR after SSM or NSM has been widened.[6] Although several studies reported the feasibility of IBR after SSM or NSM after neoadjuvant chemotherapy (NACT), IBR after NACT is still controversial.[7-9] Many patients who underwent TM after NACT showed more unfavorable clinical response or advanced stage disease before NACT. Therefore, it is difficult to compare the oncologic outcome between TM only and only those that undergo IBR after NSM or SSM group after NACT. Although an appropriate case–control study matched by clinical stage before NACT and clinical response is needed, to our knowledge, there has not yet been an appropriate matched control study.

This retrospective matched case–control study was designed to analyze oncologic outcomes between patients who underwent TM only and those who underwent IBR after SSM or NSM after NACT.

Materials and Methods

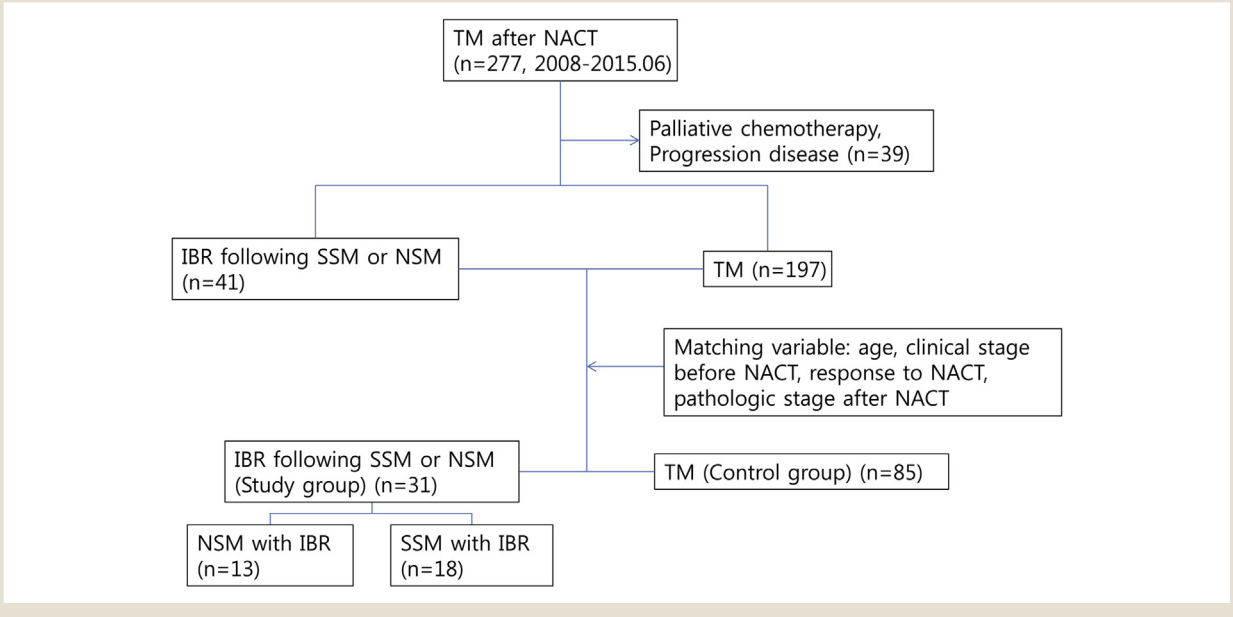
Data Collection

A retrospective review was conducted to identify all patients who underwent IBR after SSM or NSM after NACT between January 2008 and June 2015 at Samsung Medical Center, Korea. We excluded patients with distant metastasis at presentation and progressive disease during NACT in both the control and study groups. Selected patients were matched maximally 1:5 to patients who underwent TM alone after NACT. Matched variables included age, clinical stage before NACT, response to NACT, and pathologic stage after NACT. Pathologic stage followed the 7th edition of the American Joint committee on Cancer (AJCC) classification.[10] We collected clinicopathologic data from the electronic medical records. Before NACT, physical examination, magnetic resonance imaging (MRI), ultrasound (US), and mammograms were performed to access clinical disease stage. We also collected MRI and US data after NACT to assess clinical response of primary tumors and lymph nodes (LNs).

Clinical complete response was defined as the absence of evidence of a palpable tumor in the breast and/or no visible tumor on MRI and US after NACT. Partial response was defined as tumor reduction. Any increase in tumor size was considered progressive disease. All tumors that did not meet these criteria were classified as stable disease.

Locoregional recurrence was defined as tumor found within the ipsilateral chest wall (skin, subcutaneous tissue, and pectoralis muscle) or recurrence in ipsilateral axillary, supraclavicular, internal mammary, or infraclavicular LNs. Distant metastasis was defined as any recurrence in all other areas not included in locoregional recurrence. Data on recurrence events data were collected by review of electronic medical records, and survival data were acquired from the electronic medical records as well from as the Korean National Statistical Office database. All patients were treated with NACT according to the direction of the medical oncologist. Concurrent administration of trastuzumab and adjuvant trastuzumab treatment was performed according to the direction of the medical oncologist. Mastectomy was performed by a team of breast surgeons, and IBR was performed by a team of plastic surgeons. Patients whose original tumors were larger than 5.0 cm in diameter and those who had 4 or more positive axillary LNs underwent adjuvant radiotherapy.

Figure 1 Schematic Diagram of Patient Selection for Matched Study



Abbreviations: IBR = immediate breast reconstruction; NACT = neoadjuvant chemotherapy; NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy; TM = total mastectomy.

Table 1 Clinicopathologic Characteristics

Variable	Control Group (N = 85)	Study Group (N = 31)	*P*
Age (Matching Variables)			.890
≤35 years	15 (17.7)	9 (29.0)	
36-50 years	61 (71.8)	21 (67.7)	
≥51 years	9 (10.6)	1 (3.2)	
Location			.044
Right	35 (41.2)	14 (45.2)	
Left	46 (54.1)	13 (41.9)	
Bilateral	4 (4.7)	4 (12.9)	
BMI			.130
≤25 kg/m^2	62 (72.9)	28 (90.3)	
26-30 kg/m^2	18 (21.2)	2 (6.5)	
≥30 kg/m^2	5 (5.9)	1 (3.2)	
Family History			.453
Yes	5 (5.9)	4 (12.9)	
No	80 (94.1)	27 (87.1)	
Histology			.326
DCIS	2 (2.4)	3 (9.7)	
IDC	74 (87.1)	28 (90.3)	
ILC	2 (2.4)	0 (0)	
Other	7 (8.2)	0 (0)	
Multiplicity			.063
Yes	19 (22.6)	12 (40.0)	
No	65 (77.4)	18 (60.0)	
LVI			.161
Yes	33 (39.3)	17 (54.8)	
No	51 (60.7)	14 (45.2)	
NG			.317
Low	10 (11.9)	1 (3.3)	
Intermediate	27 (32.1)	14 (46.7)	
High	47 (56.0)	15 (24.2)	
ypT (Matching Variable)			.154
pT0	7 (8.2)	6 (19.4)	
pT1	29 (34.1)	15 (48.4)	
pT2	31 (36.5)	4 (12.9)	
pT3	18 (21.2)	6 (19.4)	
ypN (Matching Variable)			.494
N0	36 (42.4)	13 (41.9)	
N1	23 (27.1)	13 (41.9)	
N2	16 (18.8)	4 (12.9)	
N3	10 (11.8)	1 (3.2)	
Pathologic Stage (Matching Variable)			.939
0	7 (8.2)	3 (9.7)	
I	14 (16.5)	6 (19.4)	
II	34 (69.4)	15 (30.6)	
III	30 (35.3)	7 (18.9)	
ER Status			.608
Positive	49 (57.7)	15 (48.4)	
Negative	36 (42.4)	16 (51.6)	
PR status			.291
Positive	40 (47.1)	10 (32.3)	
Negative	45 (52.9)	21 (67.7)	
HER-2 status			.345
Amplification	29 (34.1)	10 (32.3)	
No amplification	56 (65.9)	21 (67.7)	
cT (Matching Variable)			.897
cT1	2 (2.4)	1 (3.2)	
cT2	31 (36.5)	12 (38.7)	
cT3	46 (54.1)	16 (51.6)	
cT4	6 (7.1)	2 (6.5)	
cN (Matching Variable)			.947
cN0	3 (3.5)	1 (3.2)	
cN1	20 (23.5)	10 (32.3)	
cN2	36 (42.4)	10 (32.3)	
cN3	26 (30.6)	10 (32.3)	
Response (Matching Variable)			1.000
PR	64 (75.3)	27 (87.1)	
SD	21 (24.7)	4 (12.9)	

Abbreviations: BMI = body mass index; DCIS = ductal carcinoma-in-situ; ER = estrogen receptor; HER-2 = human epidermal growth factor 2; ILC = invasive lobular carcinoma; LVI = lymphovascular invasion; NG = nuclear grade; PR = progesterone receptor.

This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the institutional review board (IRB) of Samsung Medical Center in Seoul, Korea (IRB 2016-06-082). Because this study was designed as a retrospective chart review, the need for informed consent was waived by the IRB.

Statistical Analysis

Patient characteristics were compared by weighted independent *t* tests for continuous variables and weighted chi-square or Fisher's exact tests for categorical variables. Kaplan-Meier curves, with corresponding log-rank tests, were constructed for overall survival (OS), disease-free survival (DFS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRFS). The primary end point was DFS. For all analyses, a *P* value of $< .05$ was considered statistically significant. Univariate and multivariate analysis for DFS was conducted with Cox regression for clustered matched data. All statistical analyses were performed by SAS 9.4 software (SAS Institute, Cary, NC, USA) and R 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Table 2 Characteristics of Surgical and Medical Treatment

Variable	Control Group (N = 85)	Study Group (N = 31)	*P*
Type of TM			<.0001
NSM	0 (0)	13 (41.9)	
SSM	0 (0)	18 (67.1)	
Conventional TM	85 (100)	0 (0)	
Axillary Surgery			.312
SLNB	23 (29.4)	16 (51.6)	
ALND	60 (70.6)	15 (48.4)	
Type of IBR			
TEI		20 (64.5)	
DIEP		10 (32.3)	
Others		1 (3.2)	
Adjuvant Treatment			
Trastuzumab	27 (31.8)	6 (19.4)	.032
Hormone therapy	49 (57.7)	16 (51.6)	.650
Radiotherapy	75 (88.2)	25 (80.7)	.903
NACT Regimen			.240
AC-T	75 (88.2)	29 (93.6)	
Other	10 (11.8)	2 (6.4)	

Abbreviations: AC-T = doxorubicin and cyclophosphamide followed by paclitaxel; ALND = axillary lymph node dissection; DIEP = deep inferior epigastric perforator flap; NACT = neoadjuvant chemotherapy; NSM = nipple-sparing mastectomy; SLNB = sentinel lymph node biopsy; SSM = skin-sparing mastectomy; TEI = tissue expander insertion; TM = total mastectomy.

Results

Figure 1 provides a schematic diagram of patient selection for the matched study. Among 277 patients with TM after NACT, we excluded 39 patients with distant metastasis or progression during NACT. Next, we matched by age, clinical stage before NACT, response to NACT, and pathologic stage after NACT. Overall, 31 patients who underwent IBR after SSM or NSM were included in the study group, and 85 patients who underwent TM only were included in the control group.

Patient Characteristics

The clinicopathologic characteristics of both groups are summarized in Table 1. The median age was 37 (range, 26-57) years for the study group and 40 (range, 24-56) years for the control group ($P = .890$). Median follow-up duration was 38.2 (range, 14-38) and 45.8 (range, 18-92) months for the study and control groups, respectively ($P = .012$). The median body mass index (BMI) was 22.5 (range, 18.6-36.5) kg/m^2 for the study group and 22.6 (range, 17.3-36.0) kg/m^2 for the control group. There were no significant differences between the 2 groups with respect to nuclear grade, lymphovascular invasion (LVI), age, BMI, family history, histopathology, multiplicity, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER-2) status, clinical stage before NACT, clinical response to NACT, and pathologic stage after NACT. We excluded patients with progressive disease during NACT because no patient underwent IBR after SSM or NSM, and we excluded patients with complete response after NACT because all patients underwent breast-conserving surgery. In the control group, 64 patients (75.3%) had partial response and 21 (24.7%) had stable disease. In the study group, 27 patients (87.1%) had partial response and 4 (12.9%) had stable disease.

Surgical and Medical Treatment

Surgical and medical treatments are summarized in Table 2. In the study group, 13 patients (41.9%) underwent NSM and 18 (58.1%) underwent SSM. The type of IBR depended on the patient's physical presentation and personal desires, as determined during preoperative consultations with the plastic surgeons. In the study group, 20 patients (64.5%) underwent tissue expander insertion and 10 (32.3%) underwent deep inferior epigastric perforator flap. Approximately 90% of patients were treated with a regimen based on anthracycline and taxane for NACT. Six (19.4%) and 27 (31.8%) patients in the study and control groups, respectively, received trastuzumab ($P = .240$). Twenty-five (80.7%) and 75 (88.2%) patients in the study and control groups, respectively, underwent radiotherapy ($P = .903$).

Oncologic Outcome

Two patients in the study group and 9 patients in the control group died during the study period (Table 3). Kaplan-Meier survival curves for OS (log-rank test, $P = .971$), DFS (log-rank test, $P = .520$), DMFS (log-rank test, $P = .794$), and LRFS (log-rank test, $P = .628$) are shown in Figure 2. There were no statistically significant differences in the OS, DFS, DMFS, and LRFS between the 2 groups. Univariate and multivariate analysis of DFS revealed that there was no significant difference between the 2 groups (Table 4). No recurrence was found at the nipple–areola complex and skin in the study group.

Complications

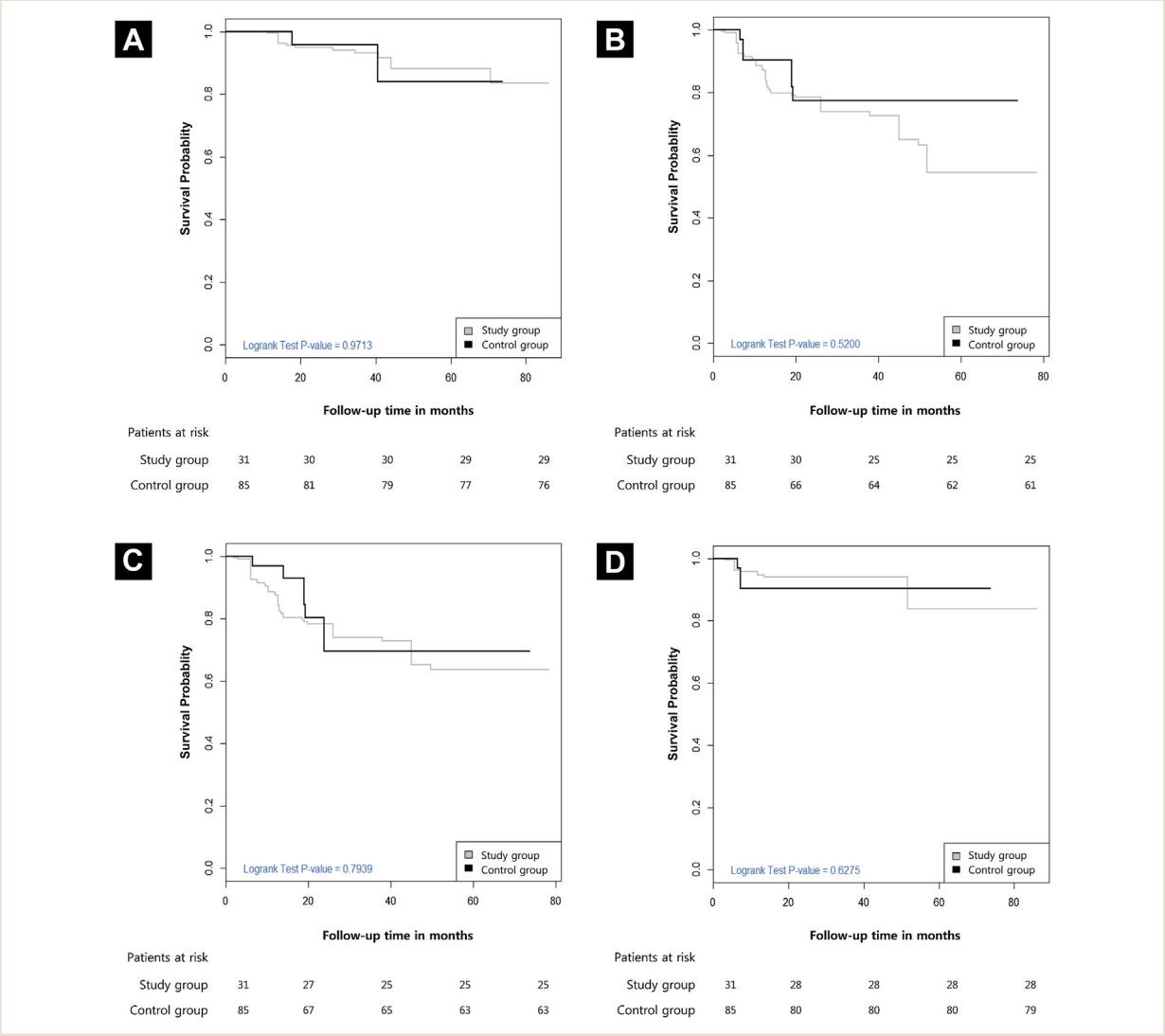
There was no statistically significant difference between the 2 groups in terms of complications ($P = .174$). Two patients in the

Table 3 Oncologic Outcomes in Study and Control Groups

Patient Group	N	Locoregional Recurrence, N (%)	Distant Recurrence, N (%)	Any Recurrence, N (%)	Death, N (%)
Study Group	31	3 (9.7)	6 (19.4)	8 (25.8)	2 (6.5)
NSM	13	0 (0)	2 (6.5)	2 (6.5)	0 (0)
SSM	18	3 (9.7)	4 (12.9)	6 (19.4)	2 (6.5)
Control group	85	6 (7.1)	22 (25.6)	24 (28.2)	9 (10.6)

Abbreviations: NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy.

Figure 2 Kaplan-Meier Survival Curves. (A) Disease-Free Survival, (B) Overall Survival, (C), Distant Metastasis-Free Survival, and (D) Locoregional Recurrence-Free Survival



Abbreviations: IBR = immediate breast reconstruction; TM = total mastectomy.

study group had complications; one patient had partial necrosis, and another patient had sclerotherapy due to uncontrolled seroma. One patient in the control group had wound infection.

Discussion

As a result of recent advances in chemotherapy and anti-human HER-2–targeted agents, the use of NACT has increased.[11] Accordingly, the number of patients who undergo IBR after NACT has also increased. The oncologic safety of IBR after SSM or NSM in patients who have advanced stage breast cancer is still controversial, especially when NACT is performed. In our study, there was no difference in DFS, LRFS, DMFS, and OS between the 2 groups after matching by age, clinical stage before NACT, response to NACT, and pathologic stage after NACT.

Several studies reported no difference in recurrence rates between TM only and IBR after SSM or NSM among patients who underwent NACT.[8,9,12-15] However, many surgeons hesitate to perform IBR after NACT because it might increase the possibility of complications, resulting in a delay in appropriate postoperative treatments such as radiotherapy or trastuzumab therapy.[13,16,17] Arnaout et al[7] was concerned that patients who underwent IBR after NACT might have increased postoperative complications, leading to a delay in adjuvant radiotherapy as well as cosmetic impairment due to radiotherapy. Aurilio et al[18] reported that IBR after SSM or NSM after NACT in patients with ER-negative disease had a significantly higher rate of local recurrence compared to the TM-only group.

In contrast, many studies showed no significant increase in complications in patients with IBR after NACT.[19-23] Song et al,[20]

Table 4 Univariate and Multivariate Analysis to Recurrence

Variable	Univariate	Multivariate	HR	95% CI	
Operation Type	0.520	0.206			
Control group (ref.)					
Study group			0.249	0.029	2.141
Age	0.0210	0.0006			
≥35 years (ref.)					
36-50 years		0.0002	0.210	0.092	0.482
≤51 years		0.0002	0.104	0.031	0.346
Family history	0.027	0.255	4.407	0.342	56.809
LVI	0.002	0.101	3.301	0.7921	13.758
Pathologic Stage	0.043	0.018			
0 (ref.)					
I		0.726	1.518	0.148	15.609
II		0.985	1.023	0.089	11.725
III		0.143	6.936	0.521	92.419
ER Status	0.029	0.063			
Positive			0.0174	0.027	1.098
Negative (ref.)					
PR Status	0.065	0.754			
Positive			0.734	0.107	5.059
Negative					

Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; LVI = lymphovascular invasion; PR = progesterone receptor.

in a meta-analysis, studied 11 of 1840 studies that showed that NACT does not increase the complication rate in patients with IBR. Nicholas et al[24] also reported no difference in 30-day postoperative overall, systemic, and surgical-site morbidity in patients who underwent IBR after SSM or NSM compared to patients who received TM alone using the American College of Surgeons National Surgical Quality Improvement Program 2005-2011 databases. Furthermore, some surgeons insisted that NACT might help reduce the possibility of postmastectomy radiotherapy because many patients experience a significant response to NACT, even though the patients were slated for radiotherapy before undergoing NACT.[25,26] In our study, there was no difference in complication between the study and control groups after NACT, consistent with the results of previous studies.

A major advantage of our study is its design. Many of the patients who underwent mastectomy after NACT had different clinicopathologic characteristics. Patients who underwent TM only after NACT tended to have more advanced-stage disease or more unfavorable clinical response during NACT than patients who underwent IBR after NACT. However, patients with IBR after NACT tended to be younger and to have a more favorable clinical stage before NACT and a better response to NACT, which is an eligibility criterion for breast-conserving surgery. Therefore, studies that simply compare oncologic outcome between TM and IBR after SSM or NSM could involve a selection bias that would affect the reliability of the result. Although a prospective randomized controlled trial is ideal, there are many difficulties associated with this because IBR is not determined by the surgeon but by patient preference, and it is hard to precisely predict the clinical response to NACT before treatment. To our knowledge, this is the first matched case–control study comparing the oncologic outcome of patients who underwent TM only and those who underwent TM after SSM or NSM after NACT. The matching analysis was considered successful not only for the matching variables but also for the other associated factors, such as LVI, multiplicity, LVI, nuclear grade, ER/PR status, and HER-2 status. This is meaningful because these factors could affect breast cancer prognosis.

Our study has several limitations. First, it is a retrospective study, and therefore this study may introduce bias; further, the follow-up duration is relatively short for accurate comparison of oncologic outcome in breast cancer. Second, we could not identify the Ki-67 score, which affects prognosis and response to NACT. Third, the sample size was too small for the accurate analysis of oncologic outcome. Finally, the median follow-up duration of the study group was shorter than that of the control group (29.2 vs. 38.8 months, respectively; $P = .012$). This difference could affect the results because of a length-of-time bias. In future studies, multicenter studies that include a larger number of patients and longer-term follow-up duration are needed.

Conclusion

IBR after SSM or NSM may be a feasible surgical treatment option for breast cancer patients who undergo NACT. Long-term follow-up data are needed to accurately evaluate oncologic outcomes.

Clinical Practice Points

- No study is available regarding a matched case–control study of NACT, so we performed one.

- Immediate breast construction may safely be performed even if patients had previously undergone neoadjuvant chemotherapy.
- Longer-term follow-up and a larger number of patients are needed to evaluate oncologic outcomes.

Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2015R1D1A1A01057585) and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI14C3418).

Disclosure

The authors have stated that they have no conflict of interest.

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