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ORIGINAL SCIENTIFIC REPORT

Feasibility of Nipple-Sparing Mastectomy with Immediate Breast Reconstruction in Breast Cancer Patients with Tumor-Nipple Distance Less Than 2.0 cm

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Abstract

Background and objective Debate continues concerning the oncological risk of nipple-sparing mastectomy (NSM) with immediate breast reconstruction (IBR) if the tumor-nipple distance (TND) is less than 2.0 cm. In this retrospective study, we analyzed oncological outcomes after NSM with IBR for the treatment of breast cancer to determine the risk posed by NSM in cases in which magnetic resonance imaging (MRI) showed a TND <2.0 cm but intraoperative frozen biopsy results were negative for tumor cells at the nipple base.

Materials and methods We conducted a retrospective review of patients with breast cancer who underwent NSM with IBR at Samsung Medical Center between 2008 and 2014. Preoperative MRI was done in all cases to define the TND, and frozen biopsy specimens were obtained intraoperatively.

Results Among the 266 NSMs performed, TND was <2.0 cm in 145 cases (54.5 %) and ≥2.0 cm in 121 cases (45.5 %). Median follow-up was 25.6 months. There were no significant differences between the two patient groups with respect to disease-free survival or local recurrence-free survival.

Conclusion Our results suggest that NSM can be a feasible treatment option when the intraoperative frozen biopsy is negative for tumor cells even with a TND <2.0 cm in MRI.

Introduction

Breast cancer is the most frequently diagnosed type of cancer and the leading cause of cancer deaths among women worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012 [1]. Recently, there has been a noticeable preference for mastectomy among patients eligible for breast-conserving surgery based on reports of an increase in breast reconstruction and prophylactic bilateral mastectomies [2]. Since the 1990s, when Toth and Lappert first introduced the skin-sparing mastectomy (SSM) [3], oncological outcomes with this procedure have been similar to those achieved with conventional mastectomy, and SSM has resulted in greater patient satisfaction and a better quality of life [4–6]. In SSM, all breast tissue is completely removed, including the nipple-areolar complex (NAC) and, in some cases, adjacent biopsy scars and skin overlying superficial tumors. By preserving the skin envelope at the time of mastectomy, this technique facilitated immediate breast reconstruction (IBR) [3].

The success of SSM has paved the way for the nipple-sparing mastectomy (NSM) in selected patients. NSM with IBR is becoming an increasingly popular choice for the surgical treatment of breast cancer. The NAC is a symbolic part of the female breast, and women who have undergone NSM have been more satisfied with the cosmetic result than have those in whom the NAC was sacrificed [7].

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Recently, a few studies have reported that patients could be considered eligible for NSM if the tumor is located within 2.0 cm of the nipple on preoperative imaging and if the frozen biopsy specimen is found to be negative for tumor cells [8, 9]. Nevertheless, many surgeons are still reluctant to perform NSM when the tumor-nipple distance (TND) is less than 2.0 cm owing to the risk for local recurrence at the NAC.

This retrospective study was designed to analyze oncological outcomes after NSM with IBR for the treatment of breast cancer in which frozen biopsy specimens were negative for tumor cells at the nipple base even though the TND was less than 2.0 cm on preoperative MRI.

Materials and methods

Patient selection

A retrospective review was conducted to identify all patients who underwent NSM with IBR between January 2008 and December 2014 at Samsung Medical Center in Seoul, Korea. All patients underwent mastectomy for the treatment of breast cancer. NSM was defined as a mastectomy that preserves the NAC, with a skin island of less than 10 cm at its largest dimension. The TND was measured as the shortest distance (in cm) between the tumor border and the base of the nipple. Patients were excluded if they had clinical evidence of NAC involvement, inflammatory breast cancer, locally advanced breast cancer with skin involvement, collagen-vascular disease, and bloody nipple discharge. However, we did not exclude patients in whom the TND was less than 2.0 cm on MRI. All patients had undergone preoperative MRI to define TND, and intraoperative frozen biopsies had been performed to confirm that the margins of resection at the nipple base were negative for tumor cells. All preoperative MRIs were reviewed by dedicated breast radiologists. In patients who had undergone neoadjuvant chemotherapy, the TND was evaluated based on MRI images obtained after neoadjuvant chemotherapy had been completed.

Pathological diagnosis

Intraoperative frozen sections were further sectioned to allow a pathological diagnosis. The same frozen biopsy sections were sectioned perpendicularly for permanent biopsy. Hematoxylin- and eosin-stained intraoperative frozen sections were reviewed by dedicated breast pathologists. NAC or nipple removal was indicated when the intraoperative frozen sections were found to be positive for invasive ductal or lobular carcinoma, lymphovascular invasion, ductal carcinoma in situ, atypical ductal hyperplasia with necrosis, or lobular neoplasia/lobular carcinoma in situ.

Neoadjuvant and adjuvant treatment

The decision to administer neoadjuvant or postoperative adjuvant chemotherapy was made in conjunction with a medical oncologist. Patients whose original tumors were larger than 5.0 cm in diameter or who had four or more positive axillary lymph nodes underwent radiation therapy.

Data collection

All specimens underwent pathological examination to determine tumor size, histopathology, nuclear grade, lymphovascular invasion, nodal status, hormone receptor status, and human epidermal growth factor receptor-2 (HER-2) expression. Demographic variables were compiled from the patients' electronic medical records and included age, body mass index, family history of breast cancer, genetic risk, type of axillary surgery, type of IBR, neoadjuvant chemotherapy, adjuvant chemotherapy/radiation therapy, locoregional recurrence (LRR), distant metastasis, and death. For patients with bilateral breast cancer, each breast was considered separately.

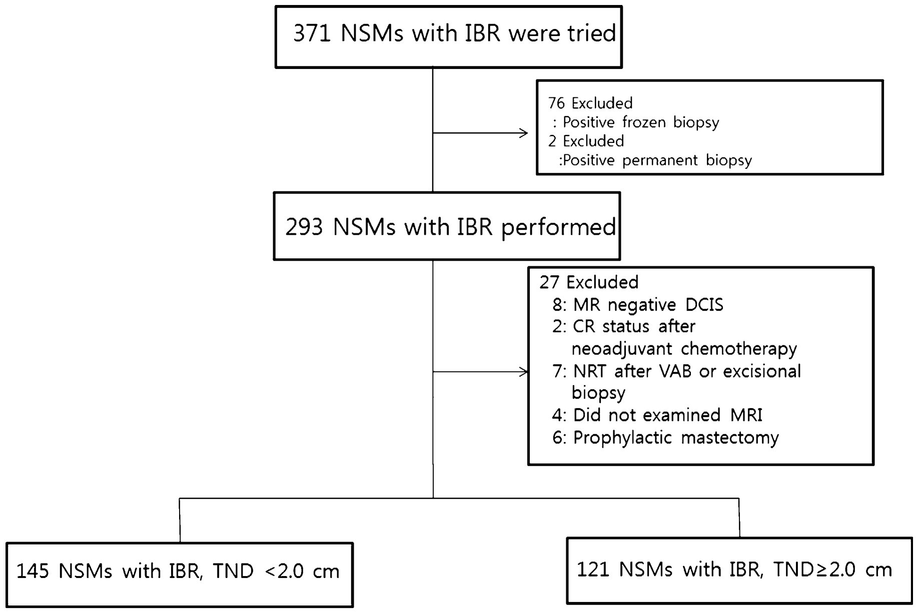
Statistical analysis

Patient characteristics were compared by means of independent t-tests for continuous variables and the Chi-square or Fisher's exact test for categorical variables. Values are reported as mean ± SD. Kaplan–Meier curves, with corresponding results of log-rank tests, were constructed for disease-free survival and local recurrence-free survival. For all analyses, a p value of <0.05 was considered statistically significant. All statistical analyses were executed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.0.3 (Vienna, Austria; http://www.R-project.org). The need for informed consent was waived because of the low risk posed by this investigation. This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the institutional review board of Samsung Medical Center in Seoul, Korea (IRB number: 2015-07-102).

Results

Figure 1 shows patient selection and exclusion criteria. For all patients scheduled NSM, underwent intraoperative frozen biopsy at the time of the initial subcutaneous dissection. The nipple or NAC was excised if the result was positive. Our institution tried to preserve the NAC in 371

Fig. 1 Flow diagram of subgroups according to tumor-nipple distance (TND)



CR, complete response; DCIS, ductal carcinoma in-situ; MRI, magnetic resonance imaging; NRT, no residual tumor; NSM, nipple sparing mastectomy; IBR, immediate breast reconstruction; TND, tumor-nipple distance; VAB, vaccum-associated biopsy

NSMs; 78 NSMs were excluded because they showed positive results just beneath the NAC at frozen biopsy ($n = 76$) and at permanent biopsy ($n = 2$), respectively, and 27 NSMs were excluded because the TND could not be clearly defined by the following: MRI-negative ductal carcinoma in situ ($n = 8$); complete response after neoadjuvant chemotherapy ($n = 2$); no residual tumor on MRI after vacuum-associated biopsy or excisional biopsy ($n = 7$); MRI not examined ($n = 4$); and no tumor found on prophylactic contralateral mastectomy ($n = 6$). Among 251 patients, 266 NSMs were performed, and 30 patients underwent therapeutic bilateral NSM. The 145 NSMs (54.5 %) in which the TND was < 2.0 cm were designated the "short TND group" (STND), and the 121 NSMs (45.5 %) in which the TND was ≥ 2.0 cm were designated the "long TND group" (LTND).

Patient characteristics

The clinicopathological characteristics of both groups are shown in Table 1. The mean age was 42.2 (±7.6) years for the STND group and 41.8 (±7.4) years for the LTND group. The mean body mass index was 21.9 (±2.7) for the STND group and 21.9 (±2.6) for the LTND group. Patients with a family history of breast cancer numbered 20 in the STND group and 15 in the LTND group. There were no significant differences between the two groups with respect to nuclear grade, lymphovascular invasion, nodal status, multiplicity, hormonal status, or HER-2 status. The overall median TND was 1.5 cm (range 0.1–7.0 cm), 0.6 and 3.0 cm for the STND and LTND groups, respectively. The STND group had smaller tumors as compared with the LTND group ($p < 0.005$). However, there was no significant difference in nodal status between the two groups ($p = 0.989$). No lymph node metastasis was found in 106 breasts in the STND group (73.1 %) and 89 breasts in the LTND group (73.5 %). Isolated tumor cell clusters, defined as small clusters of cells no greater than 0.2 mm; single tumor cells; or a cluster of fewer than 200 cells in a single histological cross section were all regarded as N0 pathologic status.

Medical treatment and follow-up

Medical treatments are shown in Table 1. There were no significant differences in the administration of neoadjuvant chemotherapy, adjuvant radiation therapy, and adjuvant hormonal therapy. The STND group had lower rates of underwent adjuvant chemotherapy as compared with the LTND group ($p < 0.005$). The mean follow-up was 25.6 months (range 1–77) which was 28.4 months (range 1–71) for the STND group and 22.2 months (range 1–77) for the LTND group, respectively.

Surgical technique

Placement of the incision was at the discretion of the breast surgeon and plastic surgeon. In 73 cases (27.4 %), the

Table 1 Clinicopathological characteristics of patients

	STND, *n* (%) *N* = 145 (54.5)	LTND, *n* (%) *N* = 121 (45.5)	*p* value
Mean age, years (±SD)	42.2 (±7.64)	41.8 (±7.44)	0.3295
Mean follow-up durations, months (range)	28.4 (1–71)	22.2 (1–77)	
BMI, kg/m^2 (±SD)	21.8 (±2.65)	21.9 (±2.62)	0.7375
Family history of breast cancer	20 (13.8)	15 (12.4)	0.7372
LVI	33 (24.3)	32 (26.9)	0.6312
NG			0.3963
Low	31 (21.4)	20 (16.5)	
Intermediate	79 (54.5)	64 (52.9)	
High	35 (24.1)	37 (30.6)	
Median TND, cm (range)	0.6 (0–1.9)	3.0 (2.0–7.0)	
Multiplicity	53 (36.5)	52 (43.3)	0.2612
Cancer stage			0.0115
In situ	46 (31.7)	18 (14.9)	
I	53 (36.5)	51 (42.2)	
II	42 (28.9)	47 (38.8)	
III	4 (2.8)	5 (4.1)	
Invasive tumor type[a]			0.0776
Ductal	88 (86.2)	89 (87.2)	
Lobular	7 (46.9)	4 (3.9)	
Mixed	3 (2.9)	4 (3.9)	
Others	4 (3.9)	5 (4.9)	
Pathologic T stage			0.002
T0	46 (31.7)	19 (15.7)	
T1	68 (46.9)	54 (44.6)	
T2	28 (19.3)	42 (34.7)	
T3	3 (2.1)	6 (5.0)	
Pathologic N stage			0.989
N0	106 (73.1)	89 (83.6)	
N1	34 (23.4)	27 (22.3)	
N2	2 (1.4)	3 (2.5)	
N3	2 (1.4)	2 (1.6)	
ER status			0.1358
Positive	124 (85.5)	95 (78.5)	
Negative	21 (14.5)	26 (21.5)	
PR status			0.0927
Positive	118 (81.4)	88 (72.7)	
Negative	27 (18.6)	33 (27.3)	
Her2-neu status			0.8939
Amplified[b]	29 (20)	25 (20.7)	
Not amplified	116 (80)	96 (79.3)	
Neoadjuvant chemotherapy	6 (4.1)	7 (5.8)	0.5349
Adjuvant treatment			
Chemotherapy	49 (33.8)	66 (55)	0.0005
Radiotherapy	17 (11.7)	17 (14.1)	0.5716
Hormonal therapy	118 (81.4)	88 (72.7)	0.2869

BMI Body mass index, *HER-2* human epidermal growth factor receptor-2, *LVI* lymphovascular invasion, *NG* nuclear grade, *SD* standard deviation, *TND* tumor-nipple distance, *ER* estrogen receptor, *PR* progesterone receptor

[a] In cases of in situ disease was excluded

[b] Her2 amplification was defined as 3+ immunohistochemistry or gene amplification in FISH

Table 2 Surgical characteristics

	STND, *n* (%)	LTND, *n* (%)	Total, *n* (%)
Axillary surgery			
SLNB	111 (76.6)	92 (76.0)	203 (76.3)
ALND	34 (23.4)	29 (24.0)	63 (23.7)
Type of IBR			
TEI	95 (65.5)	88 (72.7)	183 (68.8)
DEIP	35 (24.1)	25 (20.7)	60 (22.6)
ELD	7 (4.8)	2 (1.7)	9 (3.4)
Immediate implant insertion	5 (3.4)	4 (3.3)	9 (3.4)
TRAM	3 (2.1)	2 (1.7)	5 (3.4)

ANLD axillary lymph node dissection, *DIEP* deep inferior epigastric perforator flap, *ELD* extended latissimus dorsi flap, *IBR* immediate breast reconstruction, *SLNB* sentinel lymph node biopsy, *TEI* tissue expander insertion, *TRAM* transverse rectus abdominis myocutaneous flap

radial incision was selected, having the advantages of excellent exposure and easily controlled bleeding. In addition, the sentinel lymph node biopsy and/or axillary lymph node dissection could be performed through the lateral part of the same incision. In 80 cases (30.1 %), the lateral incision was selected. In 85 cases (32.0 %), the peri-areolar incision was selected. Subcutaneous dissection removed the maximum amount of glandular tissue while raising the NAC as a full-thickness skin flap by electrocautery. The ducts located just below the NAC were sharply excised and sent for intraoperative frozen biopsy and permanent biopsy.

Surgical characteristics

The types of axillary surgery and IBR performed are shown in Table 2. Approximately 76 % of patients underwent sentinel lymph node biopsy only. The type of IBR depended on the patient's physical presentation and personal desires, as elicited during preoperative consultations with the plastic surgeons. In both the STND and LTND groups, tissue expander insertion was the most common type of IBR.

Recurrences

A description of all events is provided in Table 3. No recurrence was found at the NAC. No patient expired after NSM. Kaplan–Meier survival curves for disease-free survival (log-rank test, $p = 0.894$) and for local recurrence-free survival (log-rank test, $p = 0.509$) are shown in Fig. 2. There were no statistically significant differences between these two groups.

Table 3 Description of events

	STND, *n* (%)	LTND, *n* (%)
Locoregional recurrence	3 (2.1)	3 (2.5)
Metachronous CBR	2 (1.3)	1 (0.8)
Distant metastasis	1 (0.7)	1 (0.8)
Death	0	0

CBC contralateral breast cancer

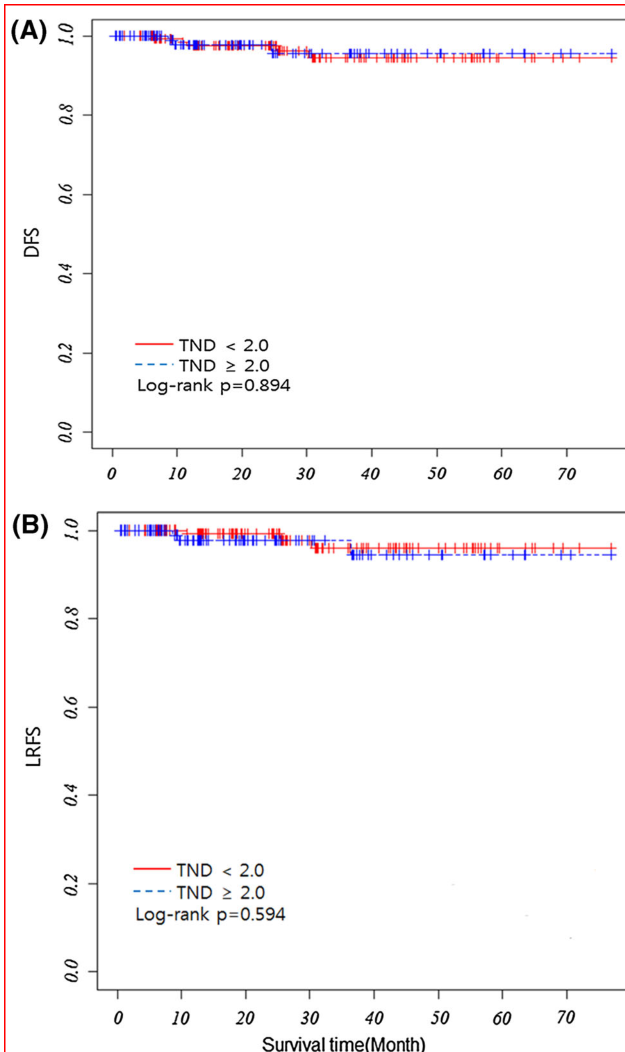


Fig. 2 Kaplan–Meier analysis of disease-free survival (DFS) (**a**) and of local recurrence-free survival (LRFS) (**b**). The two curves represent the LTND and STND groups

Postoperative complications

Table 4 summarizes the overall postoperative complications. Complications involving both the mastectomy skin flaps and the NAC were evaluated. The nipple and NAC

Table 4 Postoperative complications

Years	2008–2010	2011–2014
Number of NSMs	43	223
Complications, *n* (%)	16 (37.2)	22 (9.9)
Ischemic complications	12 (27.9)	12 (5.4)
Skin flap		
Partial necrosis	5 (11.6)	5 (2.2)
Nipple and areola		
Partial necrosis nipple	5 (11.6)	3 (1.3)
Total necrosis nipple[a]	0	1 (0.4)
Patial necrosis areola	2 (4.7)	3 (1.3)
Partial dehescence	2 (4.7)	4 (1.8)
Scar revision d/t dog ear	2 (4.7)	0
Seroma	0	1 (0.4)
Implant		
Capsular contracture	0	1 (0.4)
Infection	0	4 (1.8)

[a] Nipple excised due to total necrosis nipple

were successfully preserved except in one patient who underwent NAC excision because of total nipple necrosis. Our study showed a dramatic reduction in the rates of ischemic complications involving the NAC and nipple, from 27.9 to 5.4 %, as the surgical techniques became more refined. One patient underwent sclerotherapy because of chronic postoperative seroma formation. Two patients underwent scar revision for a "dog ear" after NSM that included a deep inferior epigastric perforator flap.

Discussion

SSM for breast cancer and prophylactic mastectomy are not new surgical procedures. In the 1960s, Freeman pioneered SSM for benign disease; however, SSM was eventually abandoned because of high complication rates and persistent questions about its oncological safety [10]. The SSM, including the NSM, has been criticized because of the increased likelihood of retained breast tissue under the skin flap and occult tumor involvement of the NAC [11–13].

Initially, many NSMs were performed as prophylactic mastectomies in women at high risk for breast cancer [14]. However, the number of primary breast cancers in residual breast tissue was higher than anticipated and raised the question of oncological risk [14]. As the surgical procedure advanced, skin flaps became thinner and the NAC flap was reduced to only 2–3 mm. Moreover, the increased accuracy of frozen biopsy results gave surgeons the confidence to perform NSM without the worry of tumor involvement at the NAC [15]. Because of these technical advances, NSM has become increasingly popular for the surgical treatment of breast cancer.

Table 5 summarizes the published studies concerning the oncological safety of NSM with IBR. The local recurrence rate is approximately 0–11 % in most series [5, 8, 9, 16–24]. These results are similar to the rates of LRR after SSM or conventional mastectomy [19, 24]. Occult tumor involvement of the NAC has been reported in 0–58 % of breast carcinomas [25, 26]. Some surgeons remain concerned about NAC recurrence as a result of occult nipple involvement; however, as shown in Table 5, NAC recurrences were only 0–3.7 %. Therefore, we could perform NSM without fear of NAC recurrence.

Exclusion criteria that contraindicate NSM are generally agreed upon and include clinical or imaging evidence of NAC involvement, locally advanced breast cancer with skin involvement, inflammatory breast cancer, and bloody nipple discharge [18, 20–22, 24, 27, 28]. Other debatable factors include tumor size, TND, positive axillary lymph nodes, previous chest wall irradiation, and previous neoadjuvant chemotherapy. Among these factors, a short TND (<2.0 cm) has been considered a major reason to avoid NSM because of the possibility of NAC involvement by residual tumor cells. Recently, however, the indication to NSM expanded including TND [8, 9, 20, 22, 29].

Initially, Warren et al. [22] excluded NSM in cases in which the TND was less than 2.0 cm on preoperative MRI. They examined MRI images only when the tumor was found to be close to the nipple on clinical examination or mammography. Over time, the inclusion criteria have been expanded. If preoperative MRI demonstrated no clear tumor involvement of the NAC, these authors performed NSM. Although 20 nipple specimens contained tumor, more than half the cases revealed negative margins on repeating excision. Others were managed with NAC radiation without nipple excision. Median follow-up was 28 months. The rate of LRR was 2.6 %, and no local recurrence at the NAC was reported.

Coopey et al. [8] also excluded NSM at first if the TND was less than 2.0 cm on preoperative MRI. However, they eventually adopted NSM even though the TND was less than 2.0 cm on MRI. This group performed 645 NSMs (330 for prophylaxis and 315 to treat breast cancer). Of the 315 NSMs for breast cancer, 28 patients (8.9 %) had a TND less than 2.0 cm on MRI and frozen biopsy results were negative for tumor cells at the nipple base. The overall mean TND was 4.0 cm (range 0–10.7). Mean follow-up was 22 months. The rate of LRR was 2.6 %, and no local recurrence at the NAC was observed. To our knowledge, this study showed the largest number of TNDs less than 2.0 cm (145 of 266 NSMs) and the shortest TND.

The intraoperative frozen biopsy is a tool commonly used to help make the decision as to whether or not to preserve the NAC. In our study, 371 frozen sections were

Table 5 A summary of published studies about oncological safety of NSM with IBR

Study	Year	Number of NSMs for breast cancer	Tumor stage	Median follow-up (months)	LRR rate (%)	NAC recurrence rate (%)	Median TND (cm)	Number of TND less than 2.0 cm
Sacchini	2006	68	0–III	25	2.9	0		11
Benediktsson	2008	216	0–III	156	21	0		
Geber	2009	61[b]	0–I	101[a]	11.7	1.6		
Petit	2009	579	0–I	19	0.9	0		
Kim	2010	152	0–IIIa	60	2	1.3		
Paepke	2009	109	T0–T3, N0	34	1.0	0		33
Jensen	2011	99		60	3.0	0		
Warren Pled	2012	428	0–III	28	2.6	0		20[d]
Sakurai	2013	788	0–IV	78	7.8	3.7		
Coopey	2013	315[b]	0–III	22[a]	2.6	0	4[c]	28
Adam	2014	69	0–IV	35	0	0	4.95[e]	5
Stanec	2014	288	0–III	63	4.1	1.2		0
Poruk	2015	105	0–IV	26[a]	0.9	0	3.58	5
Present study		266	0–III	26	2.2	0	1.50	145

LRR locoregional recurrence, *NAC* nipple-areolar complex, *NSM* nipple-sparing mastectomy

[a] Mean follow-up

[b] Number of patients underwent NSMs for breast cancer

[c] Mean TND

[d] 10 cases were managed with repeat excision (and subsequent negative margins) or nipple-areolar complex radiation

[e] Measured by MMG

obtained to evaluate the margins at the nipple base; 268 (72.2 %) were tumor-negative and 76 (20.5 %) were tumor-positive. Of the 268 tumor-negative results, 266 (99.3 %) were true negatives and 2 (0.7 %) were false negatives. Of the 76 positive results, 61 (80.3 %) were true positives and 15 (19.7 %) were false positives. The sensitivity of this examination was 96.8 % and specificity was 94.7 %, with a false-negative rate of only 3.2 %. According to these results, examination of intraoperative frozen biopsy specimens is thought to be a very accurate tool; therefore, we could consider NSM feasible when intraoperative frozen biopsy results are negative. Most of patients prefer one-stage operation in Korea, and reoperation may increase probability of delaying adjuvant treatment, such as chemotherapy or radiotherapy. Intraoperative frozen biopsy greatly reduces reoperation rate.

Although many studies have compared SSM and NSM [9, 19, 22, 24], ours is the first to compare results between a TND less than 2.0 cm and a TND of 2.0 cm or more. This study has several limitations. First, it was conducted at a single institution using a retrospective chart review, and it was relatively small in size; also, follow-up was too short to allow an analysis of overall survival. Although the follow-up data are still somewhat limited, we found similarly low rates of LRR in the two types of surgery and no NAC recurrence. Because many studies have shown that LRR peaks before 30 months after surgery, the low rate of LRR seen in our study would be expected to persist.

Recently, several studies have reported that NSM would be safe for both therapeutic and risk-reducing purposes in carriers of the BRCA1/2 mutation [30]. In our study, 10 patients (4.1 %) who underwent NSM had this mutation. Three of these patients underwent bilateral NSM because of synchronous contralateral breast cancer. The median TND for these 10 patients was 2.0 cm (range 0.1–4.7 cm). Median follow-up was 21.0 months (range 1–57). Seven of 10 patients had a family history of breast cancer. No local recurrence, including at the NAC, was observed, and there was only one case of distant metastasis. Longer follow-up of these patients is needed to determine specific LRR rates, but our results suggest that patients with the BRCA 1/2 mutation who have breast cancer could be eligible for NSM.

Conclusions

We found no difference between the short and long TND groups with respect to local recurrence or NAC recurrence in the patients treated with NSM for breast cancer. Our results suggest that NSM can be a feasible treatment option when frozen biopsy evaluation shows that the margins are free of tumor cells even though the distance between the tumor and nipple is less than 2.0 cm on MRI.

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