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ORIGINAL ARTICLE – BREAST ONCOLOGY

Recurrence Outcomes After Nipple-Sparing Mastectomy and Immediate Breast Reconstruction in Patients with Pure Ductal Carcinoma In Situ

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ABSTRACT

Background. Nipple-sparing mastectomy (NSM) has become increasingly prevalent for patients with ductal carcinoma in situ (DCIS) requiring mastectomy. However, few data regarding recurrence outcomes after NSM are available for this patient population. This study evaluated the locoregional recurrence (LRR) rate for patients with pure DCIS who underwent NSM followed by immediate breast reconstruction without adjuvant radiotherapy and investigated potential risk factors for LRR and/or nipple-areola complex recurrence (NR).

Methods. A retrospective chart review was performed for 199 consecutive patients with pure DCIS who underwent NSM and immediate breast reconstruction between March 2003 and December 2015. Risk factors for LRR and NR were analyzed using univariate (Chi square test) and multivariate (Cox model) methods.

Results. The median follow-up duration after surgery was 97 months (range, 39–186 months). At 10 years, the LRR rate was 4.5%, and the NR rate was 3%. The univariate analysis showed that high nuclear grade, negative receptor status, positive human epidermal growth factor receptor 2 (HER2) status, and negative hormone receptor/positive HER2 subtype were associated with increased risk for NR. The multivariate analysis demonstrated that negative progesterone receptor status was an independent risk factor for LRR. However, margin status and tumor-to-nipple distance (TND) were not associated with increased risk for either LRR or NR.

Conclusions. The study findings suggest that NSM can be a feasible surgical option even for DCIS with a TND of 1 cm or less if the retroareolar resection margin is negative for malignancy. Determining the molecular subtype of DCIS might be helpful in identifying patients at high risk for recurrence.

Ductal carcinoma in situ (DCIS), the most common form of preinvasive breast cancer, is characterized by the neoplastic proliferation of epithelial cells limited to the lactiferous ducts. With the widespread use and technical improvement of screening mammography, the incidence of DCIS has increased dramatically in recent decades and currently accounts for 13.2% of all new breast cancer diagnoses in Korea[1] compared with 20% in the United States.[2]

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Breast-conserving surgery (BCS) combined with adjuvant radiation therapy (RT) has become the standard treatment for DCIS. However, for approximately 30% of patients with DCIS, mastectomy still is used in cases of very diffuse lesions, multicentric disease, or an unfavorable ratio of lesions to breast volume or because of patient preference.[3]

Generally, patients treated with mastectomy for DCIS do not require further adjuvant RT because postmastectomy chest wall or skin recurrence in these patients is rare.[4] This is advantageous for an immediate breast reconstruction.[5]

Nipple-sparing mastectomy (NSM) is characterized by preservation of the entire nipple-areola complex (NAC) and breast skin envelope at the time of mastectomy, thereby facilitating superior aesthetic outcomes and improved quality of life when associated with immediate breast reconstruction.[6] Multiple nonrandomized studies have demonstrated that NSM is an appropriate procedure for carefully selected patients,[7–15] and its adoption in conjunction with immediate breast reconstruction has been increasing significantly.[16]

Given that Asian women usually have smaller breasts and relatively larger NACs than Western women, nipple-sparing techniques are important to avoiding excessive skin removal during mastectomy and facilitating immediate reconstruction. However, concerns remain regarding the oncologic safety of modern NSM for breast cancer in terms of local recurrence because long-term NAC recurrence (NR) data are limited.[17] In addition, the vast majority of NSM studies to date have included patients with both invasive and noninvasive breast cancers, as well as those who underwent prophylactic surgery.[7–14,18] However, DCIS is a clinically distinctive disease with a clinical behavior and oncologic outcome that differ from those of invasive carcinoma. Furthermore, DCIS can potentially spread widely via the branching path of the lactiferous duct in no specific pattern of microcalcification, which makes it difficult for surgeons to decide whether to preserve the nipple with a NSM procedure or not, especially for patients with a short tumor-to-nipple distance (TND).

Little data exist regarding recurrence outcomes after NSM in the setting of pure DCIS. Therefore, this study evaluated long-term locoregional recurrence (LRR) in a large series of patients with pure DCIS who underwent NSM without adjuvant RT and investigated the potential risk factors influencing LRR and NR.

METHODS

From March 2003 to December 2015, 2592 patients with DCIS underwent surgical treatment at the Asan Medical Center, Seoul, Korea. Of these, 199 consecutive patients who underwent NSM and immediate breast reconstruction were retrospectively reviewed after institutional review board approval (no. 2018-1579) was obtained. In this series, we excluded tumors with microinvasion and patients with a history of prior RT and synchronous contralateral invasive breast cancer.

The indications for NSM in this study were significant extension of DCIS compared with breast volume, multicentric disease, margin involvement in patients with DCIS after BCS, and patient preference. At our center, tumor size and TND were not considered to be contraindications to NSM. Patients with a clinically normal nipple and no skin involvement were offered the option of NSM. In all cases, a retroareolar frozen-section biopsy was collected and examined intraoperatively. The NAC was preserved if the shape, color, and palpated features of the nipple were normal and if the retroareolar ducts were confirmed to be tumor-free in the frozen-section biopsy. In the case of retroareolar ducts positive for malignancy in the intraoperative frozen section, the nipple with or without the areola was immediately removed, and the surgical procedure was converted to a skin-sparing mastectomy (SSM). If the retroareolar tissue was positive for malignancy at the final pathology, the nipple with or without the areola also was removed, and the patient was excluded from the NSM cohort.

At our center, as a matter of principle, a sentinel lymph node biopsy (SLNB) was performed for all patients who underwent mastectomy for DCIS. However, for a small proportion of patients in the current series (8.5%), SLNB was not performed either at the discretion of the treating surgeon or in the case of patients who had previously received BCS for DCIS. All the patients underwent immediate breast reconstruction via autologous or prosthetic methods by plastic surgeons.

Data on clinicopathologic characteristics, treatment, and follow-up evaluation were obtained from the prospectively maintained database of the Asan Medical Center–Breast Cancer Center (AMC-BCC). A positive surgical margin was defined as tumor touching ink in the mastectomy specimen. Postoperative follow-up evaluation included a physical examination and mammography/ultrasonography every 6 months. For patients suspected of LRR, a punch needle or excisional biopsy was performed for pathologic confirmation. Due to the retrospective nature of the study, the requirement for informed consent was waived.

The primary end point of this study was LRR as the first event, defined as ipsilateral occurrence of biopsy-proven cancerous recurrence in the chest wall, skin, NAC, or regional lymph node after NSM. For the univariate analysis of risk factors associated with LRR and NR, the Chi square test was used to compare differences between subgroups. For the multivariate analysis, a Cox proportional-hazards model was used to assess the association between the LRR rate and the multiple variables. The LRR rate was evaluated using Kaplan–Meier survival analysis. All statistical analyses were performed using IBM SPSS Statistics software version 24.0 for Windows (IBM Corp., Armonk, NY, USA). All p values lower than 0.05 were considered statistically significant.

RESULTS

Patient, Tumor, and Treatment Characteristics

A total of 199 consecutive patients with the diagnosis of pure DCIS were treated with NSM and immediate breast reconstruction. The median follow-up duration after surgery was 97 months (range, 39–186 months). Table 1 summarizes the patient, tumor, and treatment characteristics of the cohort. The median age at diagnosis was 43 years (range, 20–65 years). In the entire cohort, we confirmed that the pathologic diagnoses of both frozen and permanent biopsy sections showed no evidence of tumor involvement at the retroareolar resection margin.

For 182 NSMs (91.5%), SLNB was performed, and none (0%) were positive on frozen section biopsy. Adjuvant hormonal therapy was administered to 15 patients (7.5%) after the initial surgery, and no adjuvant RT was performed before LRR in this cohort. Autologous flap reconstruction was performed for 130 patients (65.3%), and 69 patients (34.7%) had reconstruction with an implant or tissue expander.

Recurrence Outcomes

In 10 patients (5%), LRR was identified as the first event, including 6 patients (60%) with invasive recurrence. Of these patients, five (2.5%) had isolated NR, three (1.5%) had isolated chest wall recurrence, one (0.5%) had isolated ipsilateral axillary lymph node metastasis, and one (0.5%) had NR concurrent with bilateral axillary lymph node metastases. Isolated distant metastasis as the first event was not observed. Subsequent contralateral breast cancer was observed in seven patients (3.5%).

At 10 years, the LRR rate was 4.5%, and the NR rate was 3%. The 10-year overall survival for the entire series was 98.5%. The average time to LRR was 47 months (range, 12–148 months). All the patients with chest wall or NAC recurrence underwent wide local excision. At the last follow-up evaluation, 9 of the 10 patients with LRRs were alive. The patient who presented with concurrent NR and bilateral axillary lymph node metastases died due to lung

TABLE 1 Patient, tumor, and treatment characteristics

Characteristics		*n*	%
Median age: years (range)	43 (20–65)		
	< 50	159	79.9
	≥ 50	40	20.1
Tumor size (cm)	< 4	140	70.4
	≥ 4	59	29.6
Multifocality/multicentricity	Present	61	30.7
	Absent	138	69.4
TND (cm)	≤ 1	74	37.2
	> 1	118	59.3
	Unknown	7	3.5
Margin status	Positive, ≤ 1 mm	46	23.1
	> 1 mm	153	76.9
Nuclear grade	1 ∼ 2	166	83.4
	3	31	15.6
	Unknown	2	1.0
Comedonecrosis	Positive	126	63.3
	Negative	73	36.7
ER status	Positive	173	86.9
	Negative	21	10.6
	Unknown	5	2.5
PR status	Positive	155	77.9
	Negative	39	19.6
	Unknown	5	2.5
HER2 status	Positive	47	23.6
	Negative	147	73.9
	Unknown	5	2.5
Molecular subtype	HR +/HER2–	142	71.4
	HR+/HER2+	32	16.1
	TN	5	2.5
	HR–/HER2+	15	7.5
	Unknown	5	2.5
SLNB	Yes	182	91.5
	No	17	8.5
Hormonal therapy	Yes	15	7.5
	No	184	92.5
Reconstruction methods	Autologous flaps	130	65.3
	Implant/TEI	69	34.7

TND tumor-to-nipple distance, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *TN* triple-negative, *SLNB* sentinel lymph node biopsy, *TEI* tissue expander insertion

and brain metastases after 48 months of disease-free survival.

Risk Factors for LRR and NR

In the univariate analysis, a tumor size of 4 cm or larger, high nuclear grade, negative estrogen receptor (ER) status, negative progesterone receptor (PR) status, and the hormone receptor-negative (HR–)/human epidermal growth factor receptor 2-positive (HER2+) subtype were significant risk factors for LRR. In the multivariate analysis, negative PR status was identified as the only independent risk factor for LRR ($p = 0.006$), whereas a tumor size 4 cm or larger was associated with an increased risk of LRR, with borderline statistical significance ($p = 0.064$; Table 2). High nuclear grade, negative receptor status, HER2 positivity, and HR–/HER2+ subtype were significant risk factors for NR in the univariate analysis (Table 3). Multivariate analysis was not performed for NR due to the paucity of events. In addition, a positive or close margin and a TND of 1 cm or smaller were not associated with an increased risk of LRR or NR.

DISCUSSION

To the best of our knowledge, this is the first study to assess long-term recurrence outcomes and analyze risk factors for LRR and NR after NSM without adjuvant RT in

TABLE 2 Uni- and multivariate analyses of risk factors for locoregional recurrence (LRR)

Variables		LRR no.	10-year LRR (%)	Univariate *p* value	Multivariate *p* value
Age (years)	< 50	9	5.0	0.413	
	≥ 50	1	2.5		
Tumor size (cm)	< 4	4	2.9	0.031	0.064
	≥ 4	6	8.5		
Multifocality/multicentricity	Present	1	1.6	0.146	
	Absent	9	5.8		
TND (cm)	≤ 1	5	6.8	0.444	
	> 1	5	3.4		
	Unknown	0			
Margin status	Positive, ≤ 1 mm	3	6.5	0.596	
	>1 mm	7	3.9		
Nuclear grade	1–2	6	3.0	0.031	0.469
	3	4	12.9		
	Unknown	0			
Comedonecrosis	Positive	8	5.6	0.261	
	Negative	2	2.7		
ER status	Positive	6	2.9	0.002	0.579
	Negative	4	19.1		
	Unknown	0			
PR status	Positive	4	1.9	0.001	0.006
	Negative	6	15.4		
	Unknown	0			
HER2 status	Positive	5	10.6	0.051	
	Negative	5	2.7		
	Unknown	0			
Molecular subtype	HR+/HER2–	5	2.8	0.001	0.440
	HR +/HER2+	1	3.1		
	TN	0			
	HR–/HER2+	4	26.7		
	Unknown	0			

TND tumor-to-nipple distance, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *TN* triple-negative

TABLE 3 Univariate analysis of risk factors for nipple-areola complex recurrence (NR)

Variables		NR no.	10-year NR (%)	*p* value
Age (years)	< 50	5	3.1	0.831
	≥ 50	1	2.5	
Tumor size (cm)	< 4	3	2.1	0.268
	≥ 4	3	5.1	
Multifocality/multicentricity	Present	0	0	0.098
	Absent	6	4.4	
TND (cm)	≤ 1	4	5.4	0.150
	> 1	2	1.7	
	Unknown	0		
Margin status	Positive, ≤ 1 mm	3	6.5	0.113
	> 1 mm	3	2.0	
Nuclear grade	1–2	3	1.8	0.019
	3	3	9.7	
	Unknown	0		
Comedonecrosis	Positive	5	4.0	0.302
	Negative	1	1.4	
ER status	Positive	2	1.2	< 0.001
	Negative	4	19.0	
	Unknown	0		
PR status	Positive	1	0.6	< 0.001
	Negative	5	12.8	
	Unknown	0		
HER2 status	Positive	4	8.5	0.014
	Negative	2	1.4	
	Unknown	0		
Molecular subtype	HR +/HER2–	2	1.4	< 0.001
	HR +/HER2+	0		
	TN	0		
	HR–/HER2+	4	26.7	
	Unknown	0		

TND tumor-to-nipple distance, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *TN* triple-negative

the settering of pure DCIS. In our entire cohort, the 10-year LRR rate was low (4.5%), and the 10-year NR rate also was low (3%). We found a tumor size of 4 cm or larger, high nuclear grade, ER– status, PR– status, and the HR–/HER2+ subtype were significant risk factors for LRR. High nuclear grade, negative receptor status, HER2 positivity, and the HR–/HER2+ subtype also were associated with an increased risk of NR.

Previous studies investigating DCIS have reported low LRR rates of 1% to 2.6% after mastectomy[4,19–23] and 1% to 5.9% after SSM (Table 4).[24–26] However, the literature has very little DCIS-specific data regarding LRR after NSM. Most of the published NSM series have reported recurrence rates in mixed study populations that included both invasive and noninvasive breast cancer and had varied follow-up durations. We found only two studies that focused on NSM for DCIS. However, these two studies had an insufficient number of patients (Table 4).[27,28] In 2018, Lago et al. [27] reported on 69 patients with DCIS who underwent NSM. During a mean follow-up period of 142.6 ± 70.7 months, they demonstrated an LRR rate of 11.6%, which was higher than that found in our series. However, in contrast to our series, they included patients with recurrent breast cancer after breast-conserving therapy and patients treated in the 1980s and 1990s. Although no frozen-section examination of the retroareolar margin was performed in their cohort, only one case of Paget's NR (1.4%) was observed.[27] Leclère et al. [28] reported on another NSM series of 41 patients with DCIS. However, long-term follow-up data were available for only 19 patients (46%). These 19 patients had an LRR rate of 5.3% during a mean

TABLE 4 LRR and NR after SSM or NSM for DCIS in published studies

References	No. of patients	Inclusion criteria	F/U (months)	Surgery	LRR (%)	Risk factors addressed for LRR	NR (%)	Risk factors addressed for NR
Carlson et al.[24]	223	DCIS	82	SSM	4.0	High grade	–	–
Fitzsullivan et al.[22]	469	DCIS	76	SSM	1.5	Close margin	–	–
Timbrell et al.[26]	102	DCIS, DCISM	65	SSM	5.9[a]	Age < 50 years, Close/ involved margin	–	–
Lhenaff et al.[25]	192	DCIS	120	SSM	1.6	NA	–	–
Leclère et al. [28]	19	DCIS	85	NSM	5.3	NA	5.3	NA
Lago et al. [27]	69	DCIS	143	NSM	11.6	NA	1.4	NA
Galimberti et al.[18]	278	In situ disease	94	NSM	4.0	NA	3.2	NA
Our study	199	DCIS	97	NSM	4.5[b]	PR–, ER–, HR–/ HER2+ subtype, tumor size ≥ 4 cm, high grade	3.0[c]	High grade, ER–, PR–, HER2+, HR–/ HER2+ subtype

LRR locoregional recurrence, *NR* nipple-areola complex recurrence, *SSM* skin-sparing mastectomy, *NSM* nipple-sparing mastectomy, *DCIS* ductal carcinoma in situ, *DCISM* DCIS with microinvasion, *F/U* follow-up period, *NA* not available, *PR* progesterone receptor, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

[a]5-Year LRR rate

[b]10-Year LRR rate

[c]10-Year NR rate

follow-up time of 7.1 ± 2.9 years. The only patient who experienced a recurrence had a Paget's disease recurrence in the NAC and skin 3.7 years after NSM.[28]

The current series we included a much larger cohort with pure DCIS (199 patients) who were treated at our center with NSM between 2003 and 2015. We found a 10-year LRR rate of 4.5%, which is comparable with previously reported rates of LRR after conventional mastectomy or SSM.[23,24,26] In addition, our 10-year NR rate of 3% was acceptably low, and four of the six patients with NR in our cohort presented with DCIS, Paget's disease, or both.

As previously mentioned, DCIS generally is associated with excellent outcomes, and LRR after mastectomy for DCIS is a rare event.[4] However, upstaging to invasive local recurrence is associated with increased breast cancer-specific mortality.[4,29] Identifying the clinicopathologic features of patients with a high risk of recurrence is important in consideration of patient selection, treatment, and surveillance. However, to our knowledge, no detailed data exist regarding the predictors for LRR and NR after NSM without adjuvant RT in pure DCIS, although a number of studies have attempted to identify recurrence predictors after conventional mastectomy and/or SSM in the DCIS setting with discordant results (Table 4). Fitzsullivan et al. [22] reviewed 803 patients with DCIS who underwent mastectomy and reported that eight patients (1%) experienced an LRR during a median follow-up period of 6.3 years. They found that a close margin was the only independent risk factor for LRR.[22] Owen et al. [21] reviewed 637 patients who had pure DCIS treated with mastectomy and reported 12 cases of LRR during a median follow-up period of 12 years. They found that age younger than 40 years rather than a close or positive margin was the only predictor for LRR in their univariate analysis. Carlson et al. [24] studied 223 patients treated with SSM for DCIS and reported seven cases of local (3.3%), two cases of regional (0.9%), and two cases of distant (0.9%) recurrence. The higher local recurrence rate was associated with high tumor grade, but not with age or surgical margin.[24]

Margin status is an important risk factor for local recurrence after breast-conserving therapy for DCIS found in many studies.[30,31] Several other studies have reported that positive or close margins were associated with a higher rate of local recurrence than clear margins after conventional mastectomy or SSM,[20,26,32] whereas other studies did not find that margin status correlated with an increased risk of LRR.[19,33]

In the current study, the association of margin status with LRR and NR was examined. LRR and NR were observed in 6.5% and 6.5% of the patients with positive or close margins (≤ 1 mm), respectively, and 4.6% and 2% of the patients with clear margins (> 1 mm), respectively. However, the differences in LRR and NR based on margin status were not statistically significant.

The major oncologic concern typically associated with NSM is the risk of local recurrence at the retained NAC consequent to occult nipple involvement. Numerous studies have reported that a short TND is a significant predictor for nipple involvement.[34,35] Traditionally, varied TND

cutoffs of 1 or 2 cm have been recommended by different institutions for the selection of appropriate NSM candidates.[7,8,28,36,37] However, controversy remains. Short TND is not considered a contraindication to NSM in our center. In the current study, we specifically examined the association between TND and NR after NSM. We observed NR in 4 (5.4%) of 74 patients with a TND of 1 cm or smaller and in 2 (1.7%) of 118 patients with a TND greater than 1 cm. The NR rate showed no statistical difference when the patients were stratified by TND using a cutoff of 1 cm ($p = 0.150$). The NAC was preserved if the palpation findings, shape, and color of the nipple were normal and the retroareolar ducts were confirmed to be tumor-free in the intraoperatively collected frozen-section biopsy. Our results confirmed the validity of our indications for NSM and showed an acceptably low rate of NR.

The prognostic significance of molecular biomarkers for DCIS (e.g., ER, PR, and HER2 status) and the subtypes classified by grouping of these receptors remain controversial. Williams et al.[38] reported that luminal B, HER2 type, and triple-negative DCIS were associated with increased risk of both overall and invasive recurrence compared with luminal A DCIS. Another study by Rakovitch et al. [39] reported that HER2/neu + and Ki67 + DCIS have a higher risk of noninvasive local recurrence after BCS. In contrast, other researchers found a lack of significant association between various biomarkers and risk of recurrence.[40–42]

In our study, ER status, PR status, and HR–/HER2+ subtype were associated with an increased risk of LRR, and HER2 positivity was related to a higher LRR, with borderline significance ($p = 0.051$), in the univariate analysis. Furthermore, we demonstrated that negative PR status was the only independent risk factor for LRR, whereas a tumor size of 4 cm or larger was associated with an increased risk of LRR after NSM, with borderline statistical significance, in a multivariate analysis. In addition, ER negativity, PR negativity, HER2 positivity, and HR–/HER2+ subtype were associated with an increased risk of NR in the univariate analysis.

Interestingly, studies have reported important prognostic factors for local recurrence in patients treated with BCS for DCIS.[31,38,39,43] The number of patients and LRR events in this study still may be too low for definitive statements to be made regarding risk factors for recurrence with strong statistical power. However, our results suggest that determining the molecular subtype of DCIS might be helpful in identifying patients with a high risk of recurrence and in guiding patient management. Further research with other large cohorts is needed to validate our results.

Notably, 6 of the 10 LRRs presented as NR in the current study. This finding demonstrates that NR can occur in a substantial proportion of patients with LRR after NSM for DCIS. Previous studies investigating NSM at our center also found that the presence of an extensive intraductal component (EIC) independently increases the risk of NR for patients with invasive breast cancer.[44] Petit et al. [45] also reported that the presence of an in situ lesion or an invasive carcinoma with EIC is associated with a tendency for NR to develop after NSM. These results suggest that DCIS itself seems to be associated with an increased risk of NR. Accordingly, surgeons should be mindful of the possibility of NR after NSM in this patient population. For all patients with DCIS undergoing mastectomy, SLNB should be performed because subsequent axillary lymph node mapping is not feasible for these patients. Adjuvant hormonal therapy can be considered for high-risk women to reduce the risk of NR and LRR as well as contralateral breast cancer.

CONCLUSIONS

We demonstrated an acceptably low incidence of LRR and NR during long-term follow-up evaluation in our series of patients who had pure DCIS treated with NSM and immediate breast reconstruction. Our experience suggests that NSM can be a feasible surgical option even for DCIS with a TND of 1 cm or smaller if the retroareolar resection margin is negative for malignancy. Additionally, determining the molecular subtype of DCIS might help in identifying patients at a high risk for recurrence.

DISCLOSURE There are no conflicts of interests.

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