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ORIGINAL ARTICLE

Oncologic safety of skin-sparing mastectomy followed by immediate reconstruction in young patients with breast cancer☆

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Summary *Backgrounds:* This study aimed to compare the oncologic outcomes of nipple-sparing mastectomy (NSM)/skin-sparing mastectomy (SSM) followed by immediate reconstruction with those of conventional mastectomy (CM) in young patients aged under 35 years old with breast cancer.
Methods: We analyzed retrospectively 2889 patients who underwent mastectomy for breast cancer at Asan Medical Center from January 2003 to December 2008. We compared NSM/SSM followed by immediate reconstruction with CM in patients under 35 years old by analyzing clinicopathologic features, breast cancer specific survival rate (BCSS), distant metastasis free survival rate (DMFS), and local recurrence rate (LRR).
Results: Out of a total of 2889 patients, we performed NSM/SSM in 118 patients and CM in 141 patients aged less than 35 years old. DMFS were 85.3% and 73.4% in NSM/SSM and CM, respectively ($p = 0.001$). BCSS were 90.7% and 73.0% in NSM/SSM and CM, respectively ($p = 0.001$). After adjusting for stage, there were no statistically significant differences between the two groups with respect to DMFS and BCSS. The type of surgery was not a prognostic factor in multivariate analysis for DMFS and BCSS (CM vs. NSM/SSM: DMFS HR = 0.67, $p = 0.215$; BCSS: HR = 0.66, $p = 0.265$).

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Conclusions: Compared to CM, NSM/SSM followed by immediate breast reconstruction is oncologically safe and could be a viable surgical treatment in young patients under 35 years old with breast cancer.

1. Introduction

Breast cancer is uncommon in women younger than 35 years of age. In Western countries, fewer than 4% of breast cancer diagnoses involve women less than 35 years old.[1,2] In Korea, however, more than 10% of newly diagnosed breast cancer patients are younger than 35 years old.[3,4] Women younger than 35 years with breast cancer face some specific problems that are less relevant for older premenopausal patients, including the late effects of radiation therapy, pregnancy after treatment, and interpersonal, family and professional relations.[5] Hence, special consideration should be given to patients in this age group. Although some results have indicated the contrary, many studies show that breast cancer arising in younger females is more aggressive and associated with an unfavorable prognosis.[4,6–11] In previously published reports, tumors in younger were of a higher grade, and had a higher proliferating fraction and more vascular invasion than those in older patients.[1,12,13]

Young patients are distressed not only by breast cancer but also by their body image after cancer surgery. Therefore, they are more interested in breast reconstruction than older patients. The surgical techniques of nipple-sparing mastectomy (NSM) or skin-sparing mastectomy (SSM) followed by immediate reconstruction in patients with breast cancer are associated with superior cosmesis and higher patient satisfaction. There have been recent studies demonstrating the oncological safety of NSM or SSM with immediate breast reconstruction.[14–17] However, there are few studies about oncologic outcomes in young patients, especially in those under 35 years old, after NSM or SSM followed by immediate reconstruction. Because of the limited number of patients and the lack of clinical trials using young females with breast cancer, both clinicians and patients do not have enough information to make informed decisions about the optimal treatment, including the type of surgery.

This study was performed to compare the oncologic outcomes of NSM or SSM followed by immediate reconstruction with those of conventional mastectomy (CM) in young women ($\leq$35 years old) with breast cancer.

2. Patients and methods

2.1. Subjects

We analyzed retrospectively 7127 patients with breast cancer who underwent surgery at Asan Medical Center from January 2003 to December 2008. Exclusion criteria were follows: neoadjuvant systemic therapy, carcinoma in situ, distant metastasis at the time of diagnosis, short follow-up period ($<$6 months), breast conserving surgery, and axillary operation alone. Out of a total of 2971 patients who underwent mastectomy for breast cancer, 2214 underwent CM and 757 underwent NSM/SSM followed by immediate reconstruction. Patients with clinical stage I to III breast cancer were offered the option of NSM or SSM followed by immediate reconstruction as an alternative to CM. However, we included patients who underwent immediate transverse rectus abdominis musculocutaneous (TRAM) flap reconstruction. Finally, 675 patients who underwent NSM/SSM followed by TRAM were enrolled in this study (Fig. 1). The surgical method was decided according to the patient 's decision requiring total mastectomy. Also, reconstruction method was decided according to the plastic surgeons' decision.

Among the 2889 patients with breast cancer, 259 patients were under 35 years old; 141 underwent CM and 118 underwent SSM (59 patients)/NSM (59 patients) followed by immediate TRAM flap reconstruction.

We reviewed medical records and pathologic factor and tumor staging followed the tumor-node-metastasis classification of the American Joint Committee on Cancer.[18] This study was reviewed and approved by the Institutional Review Board of Asan Medical Center (20150049).

2.2. Statistical analysis

Distant metastasis free survival (DMFS) was defined as the time from surgery to the first appearance of distant metastasis. Breast cancer-specific survival (BCSS) was defined as the time from surgery to the time to death for breast cancer cause. Correlations between surgical method and several variables were evaluated using the chi-square test, and the means of continuous variables such as age among different groups were compared using ANOVA test. Survival curves were generated using the Kaplan–Meier method, and the significance of survival differences among selected variables was verified using the log-rank test. The Cox proportional-hazards model was used to evaluate the independent prognostic effect of surgical method on DMFS and BCSS. To correct for different demographic and clinical factors in the 2 cohorts, we performed 1:1 propensity score (PS) matching between the CM and NSM/SSM cohorts. Statistical analysis was made using SPSS version 18.0 (SPSS, Chicago, IL, USA) with a significance level of $p < 0.05$.

3. Results

3.1. Patient characteristics

We analyzed 2889 enrolled patients. Of these, 259 were under 35 years old and 2630 were over 35 years old. BMI ($p < 0.001$), lymphovascular invasion ($p = 0.015$), and

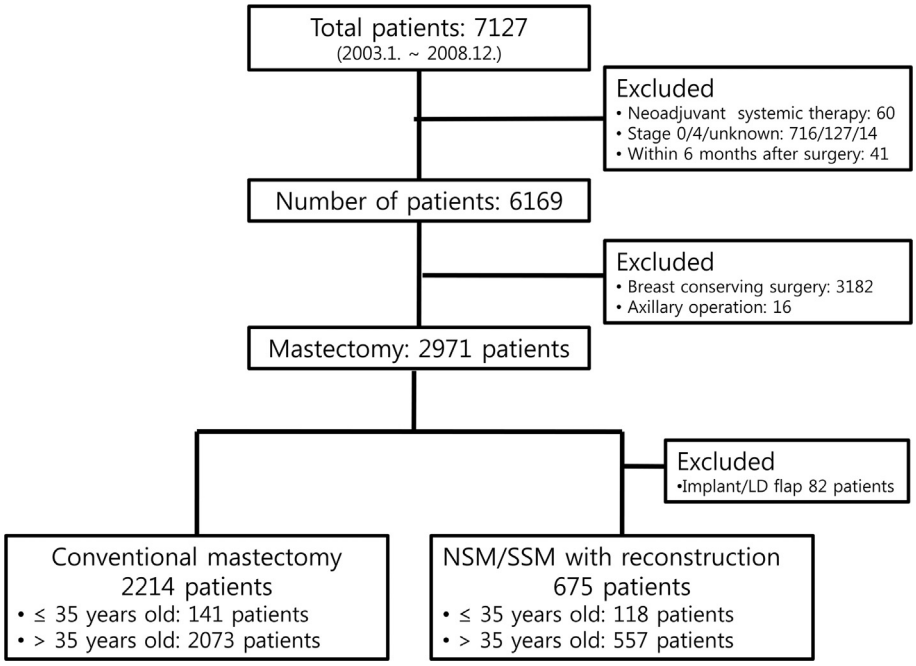

Figure 1 Distribution of enrolled patients (total 2889 patients).

progesterone receptor positivity ($p = 0.030$) were lower in younger patients. The rates of LN metastasis and triple negative breast cancer were higher in younger patients ($p = 0.011$ and $p = 0.044$, respectively). Younger patients underwent chemotherapy ($p < 0.001$) and radiation therapy ($p = 0.024$) more frequently than older patients. There were no statistically significant differences in other factors (Supplementary Table 1).

Table 1 shows the clinicopathologic features of the 259 patients aged under 35 years old; 118 (45.6%) underwent NSM/SSM with reconstruction and 141 (54.4%) underwent CM. There was a statistically significant difference in BMI between the two patient groups ($p = 0.003$). The NSM/SSM with reconstruction group had earlier stage disease ($p < 0.001$), smaller tumor size ($p < 0.001$), less node metastasis ($p < 0.001$), lower HG ($p < 0.001$), lower NG ($p < 0.001$), less lymphovascular invasion ($p < 0.001$), and higher progesterone receptor positivity ($p = 0.007$) than the CM group. The rates of triple negative breast cancer were higher in the CM group ($p = 0.004$). The CM group underwent chemotherapy and radiation therapy more frequently than the NSM/SSM with reconstruction group ($p < 0.001$).

3.2. Survival analysis

We performed survival analysis in 259 young patients under 35 years old. The median follow-up durations for NSM/SSM with reconstruction and CM were 86.7 and 88.0 months, respectively.

The 5-year DMFS were 85.3% and 73.4% in the NSM/SSM with reconstruction group and CM group, respectively (log-rank $p = 0.001$). The 5-year BCSS were 90.7% and 73.0% in the NSM/SSM with reconstruction group and CM group, respectively (log-rank $p = 0.001$, Fig. 2). In the survival analysis according to stage, there were no statistically significant differences between the two groups with respect to DMFS and BCSS outcomes at each stage (Figs. 3 and 4).

We performed univariate and multivariate analysis to identify the factors influencing survival differences between two groups. In univariate analysis, the factors influencing DMFS were as follows: tumor size over 2 cm ($p < 0.001$), node metastasis ($p < 0.001$), higher stage (Stage II; $p = 0.002$, Stage III; $p < 0.001$), lymphovascular invasion ($p = 0.002$), CM ($p < 0.003$), chemotherapy ($p = 0.047$), and radiation therapy ($p = 0.030$) (Supplementary Table 2). The factors associated with BCSS were as follows: node metastasis ($p = 0.001$), higher tumor stage (Stage II; $p = 0.017$, Stage III; $p = 0.001$), higher NG ($p = 0.045$), and CM ($p = 0.002$).

In multivariate analysis, the factors influencing DMFS were tumor size over 2 cm ($p = 0.018$) and node metastasis ($p = 0.004$). On the other hand, node metastasis ($p = 0.010$) was the only factor associated with BCSS (Table 2). The type of surgery was not a prognostic factor in multivariate analysis for DMFS and BCSS (CM vs. NSM/SSM: DMFS $p = 0.215$; BCSS: $p = 0.265$). To overcome selection bias, we performed 1:1 propensity score (PS) matching between the CM and NSM/SSM cohorts. After PS matching, 65 patients were included in each group. The CM and NSM/SSM groups were well matched for age at diagnosis, BMI, stage, histologic grade, nuclear grade, ER, PR, LVI, HER-2 status, and adjuvant treatment including chemotherapy, hormonal therapy, and radiotherapy. Despite PS matching, there were no statistically significant differences between the two groups with respect to DMFS and BCSS outcomes (DMFS: $p = 0.306$; BCSS: $p = 0.107$; Supplementary Fig. 1).

3.3. Local recurrence

Local recurrence was observed in 12 (10.2%) of 118 patients who underwent NSM/SSM with reconstruction and in nine (6.4%) of 141 patients who underwent CM (Table 1). The 5-

Table 1 Clinicopathologic characteristics of the young patients (≤35 years old) with breast cancer.

Factors		NSM/SSM with reconstruction (N = 118)	Conventional mastectomy (N = 141)	p-value
		N (%)	N (%)	
Age at diagnosis (years)	Median (range)	33.0 (23–35)	33.0 (24–35)	0.997
BMI (kg/m^2)	<18.5	8 (6.8)	16 (11.4)	0.003
	18.5–22.9	83 (70.3)	67 (47.9)	
	23–24.9	16 (13.6)	29 (20.7)	
	≥25	11 (9.3)	28 (20.0)	
	Unknown		1	
Stage	I	54 (45.8)	14 (9.9)	<0.001
	II	50 (42.4)	67 (47.5)	
	III	14 (11.9)	60 (42.6)	
Tumor size, cm	≤2	71 (60.2)	36 (27.5)	<0.001
	>2	47 (39.8)	95 (72.5)	
	Unknown		10	
Nodal status	Negative	69 (60.0)	37 (37.6)	<0.001
	Positive	46 (40.0)	97 (72.4)	
	Unknown	3	7	
Histologic grade	G1/2	76 (72.4)	60 (44.8)	<0.001
	G3	29 (27.6)	74 (55.2)	
	Unknown	13	7	
Nuclear grade	G1/2	78 (69.6)	58 (43.6)	<0.001
	G3	34 (30.4)	75 (56.4)	
	Unknown	6	8	
Lymphovascular invasion	Negative	83 (72.8)	66 (49.6)	<0.001
	Positive	31 (27.2)	67 (50.4)	
	Unknown	5	7	
Estrogen receptor	Negative	47 (39.5)	68 (48.9)	0.097
	Positive	72 (60.5)	71 (51.1)	
	Unknown		1	
Progesterone receptor	Negative	58 (48.4)	90 (64.7)	0.007
	Positive	61 (51.3)	49 (35.3)	
	Unknown		1	
HER2(IHC)	Negative	72 (60.5)	96 (70.1)	0.089
	Positive[a]	47 (39.5)	41 (29.9)	
	Unknown		3	
Subtype	HR+ [b]/HER-	56 (47.5)	53 (38.4)	<0.004
	HR+/HER2+	22 (18.6)	21 (15.2)	
	HR−/HER2+	25 (21.2)	20 (14.5)	
	HR−/HER2−	15 (12.7)	44 (31.9)	
	Unknown		3	
Chemotherapy	Yes	93 (78.2)	133 (95.0)	<0.001
	No	26 (21.8)	7 (5.0)	
	Unknown		1	
Radiation therapy	Yes	17 (14.3)	68 (48.6)	<0.001
	No	102 (85.7)	72 (51.4)	
Antihormonal therapy	Yes	80 (67.2)	83 (60.1)	0.180
	No	39 (32.8)	55 (39.9)	
	Unknown		2	
Local recurrence		12 (10.2)	9 (6.4)	0.360

HER2, Human Epidermal growth factor Receptor-2; IHC, immunohistochemistry; HR, hormone receptor.
[a] IHC 3+.
[b] Estrogen receptor positive or Progesterone receptor positive.

year local recurrence-free survival rate were 91.3% and 92.4% in the NSM/SSM with reconstruction group and CM group, respectively (log-rank $p = 0.427$). These local failure rates were similar between two groups (Fig. 5). We performed analysis of local recurrences to detect differences according to stage and subtype in each group. However, the risk of local recurrence did not increase significantly according to stage in either group. Also, there were no statistically significant differences according to subtype in each group (Supplementary Figs. 2 and 3).

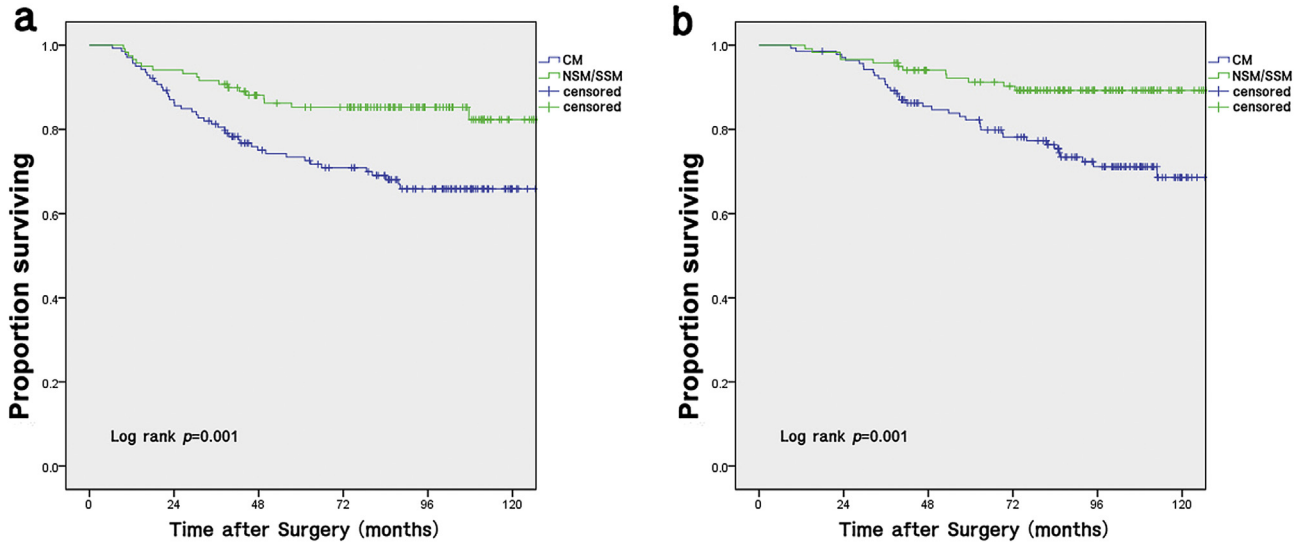

Figure 2 Survival curves for NSM/SSM with reconstruction and CM in 259 patients (≤35 years old). a Distant metastasis-free survival. b Breast cancer-specific survival.

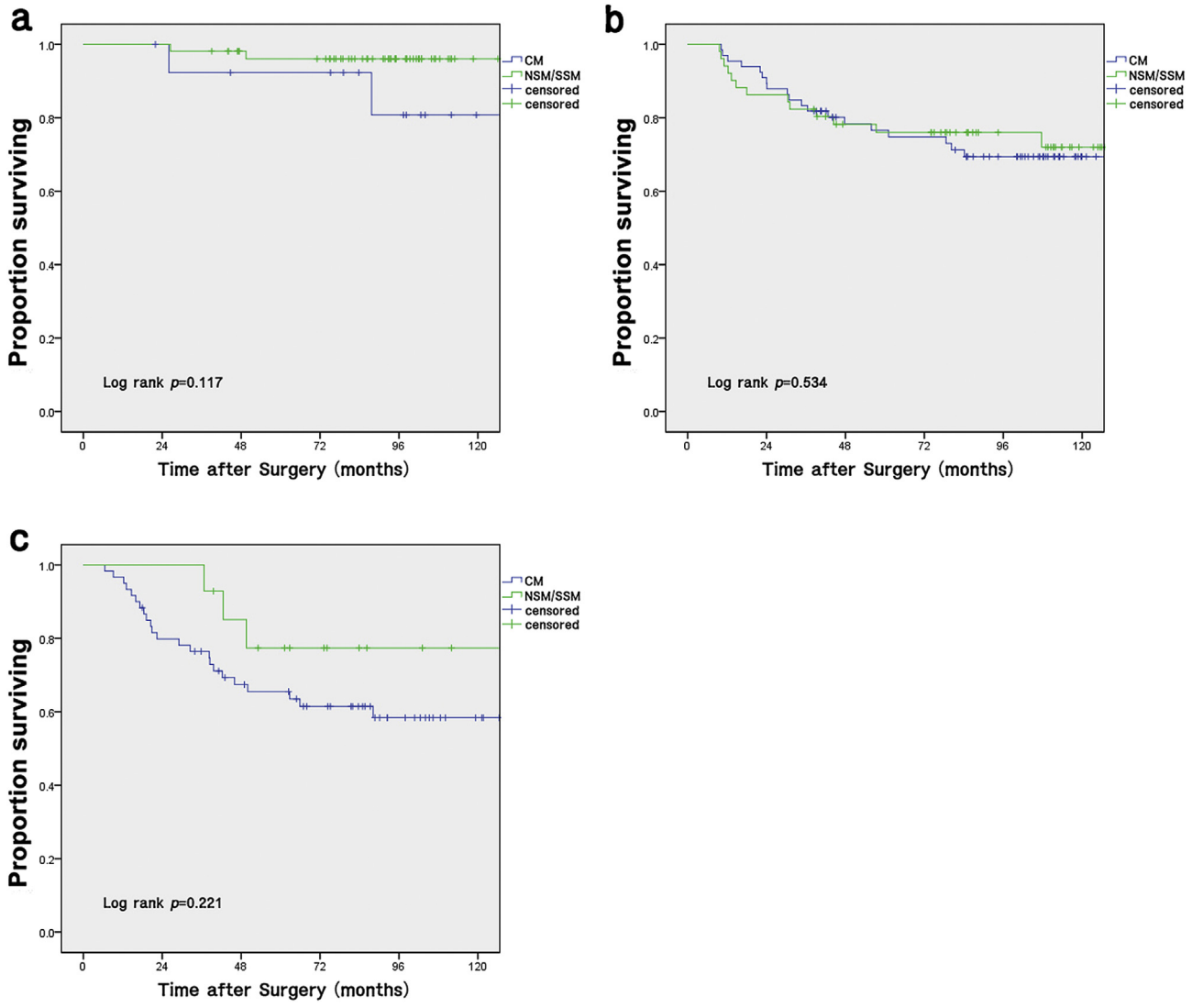

Figure 3 Distant metastasis-free survival curves for NSM/SSM with reconstruction and CM in 259 patients (≤35 years old) by stage. a Stage I, b Stage II, c Stage III.

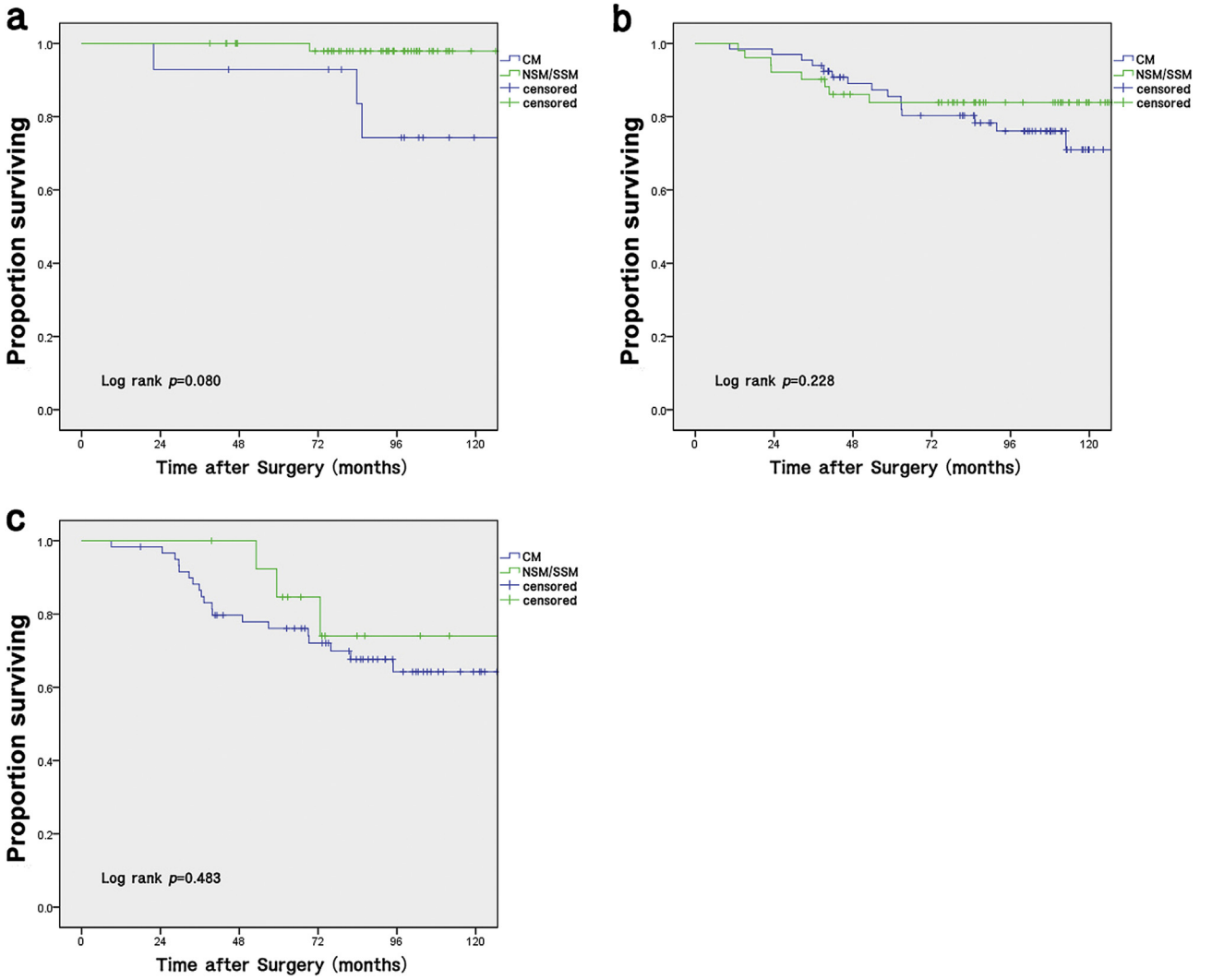

Figure 4 Breast cancer-specific survival curves for NSM/SSM with reconstruction and CM in 259 patients (≤35 years old) by stage. a Stage I, b Stage II, c Stage III.

4. Discussion

The term skin-sparing mastectomy was first introduced by Freeman in 1962 and modified by Toth and Lappert in 1991 to describe the complete removal of the breast through a well-planned incision that maximized the preservation of the skin envelope of the breast and provided an improved cosmetic result when combined with immediate breast reconstruction.[14,19,20] SSM followed by immediate breast reconstruction for the surgical treatment of early-stage breast cancer has become a common and widely used procedure over the past decade.[21] Furthermore, the nipple—areola complex can be preserved during SSM in patients with negative subareolar frozen section findings. Compared to CM followed by delayed reconstruction, NSM/SSM followed by immediate reconstruction had the advantages of reducing the patient's emotional trauma following the loss of a breast, achieving better cosmetic outcomes, and increasing cost-effectiveness.[22,23]

Breast cancer is uncommon in women younger than 35 years of age, where it accounts for fewer than 4% of the total number of breast cancer cases diagnosed in Western countries.[2,24] However, in Asian breast cancer patients, the proportion of patients in this age group was reported to be much higher (ranging from 9.5% to 12%).[3] In our study, the median age of the patients was 47 years old and the percentage of young patients under 35 years old was 7.4% (data not shown). In general, younger patients are more concerned about their body image than older patients. Actually, a recent study showed that women under 40 years of age are significantly more likely to undergo mastectomy followed by breast reconstruction than breast conserving therapy compared with older women.[25]

The young age (under 35—40 years old) of breast cancer patients has been proposed to be an independent prognostic factor of poor survival in some studies.[4] In previously published reports, tumors in younger women have usually been shown to be hormone receptor negative, of higher grade, with a higher proliferating fraction, and more vascular invasive, and to have higher expression of Ki-67 and p53, than tumors in older patients.[1,9,13]

Table 2 Multivariate analysis for distant-metastasis-free survival (DMFS) and breast-cancer-specific survival (BCSS) in 259 young patients (≤35 years old) with breast cancer.

Factors	DMFS			BCSS		
	HR	95% CI	p-value	HR	95% CI	p-value
Tumor size (>2 cm vs. ≤2 cm)	2.64	1.18–5.86	0.018	1.16	0.55–2.44	0.707
Node status (positive vs. negative)	3.65	1.52–8.76	0.004	3.66	1.36–9.84	0.010
HG (G3 vs. G1,2)	0.71	0.37–1.39	0.323	1.10	0.53–2.27	0.806
Hormone receptor (negative vs. positive[a])	3.04	0.35–26.28	0.313	3.78	0.31–45.80	0.296
Tissue HER2 (positive[b] vs. negative)	1.12	0.60–2.08	0.718	0.85	0.49–1.85	0.874
Surgery (CM vs. NSM/SSM)	0.67	0.36–1.26	0.215	0.66	0.31–1.38	0.265
Chemotherapy	1.15	0.23–5.65	0.868	0.51	0.06–4.27	0.530
Antihormonal therapy	5.10	0.61–42.55	0.133	5.07	0.43–59.60	0.197
Radiation therapy	1.24	0.68–2.29	0.483	1.02	0.51–2.03	0.957

HR, hazard ratio; CI, confidence interval; Human Epidermal growth factor Receptor-2; IHC, immunohistochemistry.
[a] Estrogen receptor positive or Progesterone receptor positive.
[b] IHC3+; NSM, Nipple sparing mastectomy; SSM, Skin sparing mastectomy; CM, Conventional mastectomy; vs., versus.

Because of the reasons mentioned above, we performed an analysis in patients under 35 years old with breast cancer who underwent NSM/SSM followed by immediate reconstruction. In our study, younger patients more often underwent NSM/SSM with reconstruction than older patients (>35 years old) ($p < 0.001$). Also, younger patients had more often poor prognostic factors than patients over 35 years old.

We performed an analysis to compare the oncologic outcomes between NSM/SSM with reconstruction and CM in patients under 35 years old. The NSM/SSM with reconstruction group had better prognostic factors. This may suggest selection bias resulting from the patients in this group wanting to avoid adjuvant radiotherapy, which can have a negative influence on cosmetic outcomes. In fact, the NSM/SSM with reconstruction group received less radiation therapy than the CM group ($p < 0.001$).

The NSM/SSM with reconstruction group showed better DMFS ($p < 0.001$) and BCSS outcomes ($p < 0.001$) than the CM group. Factors influencing DMFS were tumor size, node metastasis, stage, lymphovascular invasion, type of surgery, chemotherapy, and radiation therapy, according to

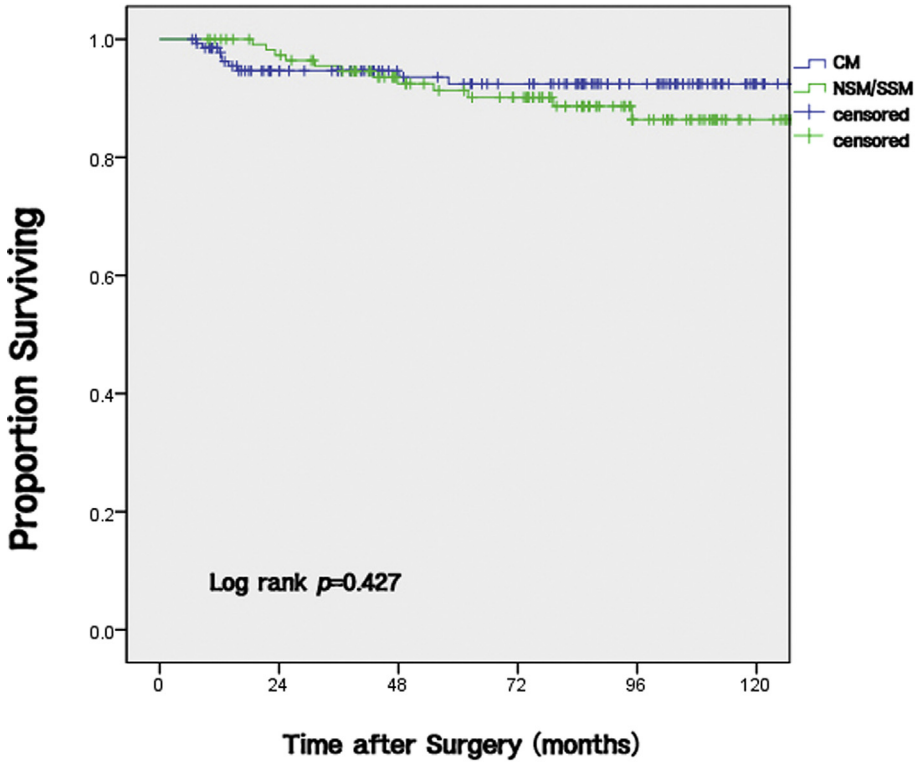

Figure 5 Local recurrence-free survival curves for NSM/SSM with reconstruction and CM in 259 patients (≤35 years old).

univariate analysis. However, in multivariate analysis, the type of surgery was not a prognostic factor in multivariate analysis for DMFS and BCSS. After adjusting for stage, there were no statistically significant differences between the two groups with respect to DMFS and BCSS at each stage. Several meta-analyses have concluded that SSM with reconstruction is an oncologically safe procedure, at least for patients with early-stage disease and a small tumor.[26,27] However, comparable results have also been obtained for patients with stage III disease. Despite the relatively small number of patients with stage III disease in this study, our findings strengthen the opinion that NSM/SSM followed by immediate TRAM flap reconstruction may be suitable for patients with advanced-stage disease.[16]

Several studies report no significant differences in recurrence patterns or incidences between patients undergoing SSM and those undergoing CM.[16,28] In 2009, Gerber et al provided almost 10 years of extended follow-up data and concluded that NSM is oncologically safe; only one nipple areola complex (NAC) recurrence out of 112 NSMs was observed, and there was no statistical significance between overall local recurrence (LR) between NSM and CM.[29] In our study, the LRRs were 10.2% in patients under 35 years old who underwent NSM/SSM with reconstruction. However, there was no statistically significant difference compared to CM ($p = 0.360$). Furthermore, there were no statistically significant differences between each group with respect to stage and subtype.

Although the present study involved retrospective analysis, it included patients aged less than 35 years old and involved a single institute. Moreover, the patients in the present study were not selected relatively, and this study analyzed patients with only one type of TRAM reconstruction. There is almost no cosmetic difference between the various reconstruction methods immediately after the operation, but the possibility of side effects due to deformation of the implant increases over time. In addition, asymmetrical differences with the operated breast may occur due to the natural aging of the normal breast without surgery. The use of one type of reconstruction method can provide a more thorough view of this treatment method.

In conclusion, our study showed that NSM/SSM does not pose a higher risk of local, regional, or systemic recurrences over that of CM in the young patients with breast cancer. The procedure is oncologically safe and provides a superior cosmetic outcome. NSM/SSM followed by immediate reconstruction should therefore be considered standard of care for patients undergoing mastectomy when immediate reconstruction is used in the young patients with breast cancer.

Conflicts of interest

The authors do not have any conflicts of interests to disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.04.004.

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