Oncological safety of nipple-sparing mastectomy in young patients with breast cancer compared with conventional mastectomy

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Abstract. Although nipple-sparing mastectomy (NSM) is being used more frequently, the oncological safety of NSM remains unclear, particularly in young patients (<35 years). The aim of the present study was to compare the rates of local recurrence (LR), disease-free survival (DFS) and overall survival (OS) in young patients with breast cancer who had undergone NSM or conventional mastectomy (CM). The clinicopathological data of young patients with stage 0-IIB breast cancer who had undergone NSM (163 cases) or CM (194 cases) between 2007 and 2016 were retrospectively analyzed. The log-rank test was used to analyze the differences in the LR, DFS and OS rates between the two groups and multivariate analysis was used to analyze the patient prognostic factors for DFS. The median follow-up time was 49 months. Patients who had undergone CM were more likely to exhibit stage II disease (68.4 vs. 58.3%; P=0.015) and positive lymph nodes (45.9 vs. 33.1%; P=0.014). In the NSM group, LR occurred in 7 (4.3%) cases, systemic recurrence in 15 (9.2%) cases and mortality in 9 (5.5%) cases. In the CM group, LR occurred in 6 (3.1%) cases, systemic recurrence in 27 (13.9%) cases and mortality in 15 (7.7%) cases. There were no statistical differences in the LR, DFS and OS rates between the two groups (P>0.05). Following adjustment for clinical stage, the LR and DFS rates between the two groups exhibited no significant differences. Analysis of the prognostic factors demonstrated that clinical stage, lymph node status, estrogen and progesterone receptor status and human epidermal growth factor receptor 2 status were associated with DFS (P<0.05). NSM is safe for young patients with early-stage breast cancer and provides patients with an improved cosmetic outcome. Furthermore, nipple-areola complex preservation does not increase the risk of recurrence.

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Introduction

In the 1800s, Halsted first practiced and standardized radical mastectomy (RM) (1). Subsequently, surgery for breast cancer has significantly improved with regards to oncological safety and cosmetic outcome. In 1965, Madden (2) first introduced modified RM (MRM), which has since been frequently performed clinically. RM and MRM are grouped with conventional mastectomy (CM), and the local recurrence (LR) rate following CM was ~10% 10 years after surgery (3-5).

In 1991, Toth and Lappert (6) first described skin-sparing mastectomy (SSM), which involves removing the mammary glands, including the nipple-areola complex (NAC), while preserving the native skin envelope and the inframammary fold. The oncological safety (local disease control) of SSM has been demonstrated to be equivalent to that of MRM (7,8). Nipple-sparing mastectomy (NSM) is similar to SSM, but does not involve removal of the NAC (9). In 1984, Hinton *et al* (10) first reported that the LR and survival rates following NSM was equivalent to those following MRM; however, this conclusion was not accepted by prominent surgeons at the time due to the fact that the NAC may harbor occult tumor cells, thereby increasing the risk of LR (11,12). Previous studies have reported NAC involvement in 5-12% of cases (13,14). Over time, an increasing number of studies have reported that NSM may provide oncological safety compared with CM for carefully selected patients (15-19).

The young age of certain patients has been revealed to be associated with a poor prognosis and an increased risk of LR in breast cancer (20-22), an effect which may be explained, in part, by diagnosis at a later stage and a higher proportion of unfavorable tumor characteristics (23-25). Although young age was previously a contraindication for breast-conserving surgery (BCS), later studies have reported that young

patients who had undergone BCS may exhibit oncological safety compared with those who had undergone CM (26). Bantema-Joppe *et al* (27) reported that the 10-year overall survival (OS) rate of patients following BCS was not impaired, compared with traditional mastectomy in young patients with early-stage breast cancer. Furthermore, the oncological safety of NSM in young patients with breast cancer has rarely been reported and remains poorly understood.

In the present study, LR, disease-free survival (DFS) and OS rates were investigated in young patients with early-stage breast cancer who had undergone NSM or CM.

Materials and methods

Data collection. The information of young patients with stage 0-IIB breast cancer who had undergone NSM (163 cases) or CM (194 cases) at Guangxi Medical University Affiliated Tumor Hospital (Nanning, China; 103 NSM cases and 126 CM cases) and Liuzhou People's Hospital (Liuzhou, China; 60 NSM cases and 68 CM cases), between January 2007 and June 2016, was collected. Patient clinicopathological data were collected, including age at diagnosis, tumor size, nodal status, Tumor-Node-Metastasis (TNM) stage (28), histological grade, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER-2) expression, surgical procedures, complications and adjuvant treatment regimens. Follow-up data included LR time, systemic recurrence time and patient mortality.

Inclusion and exclusion criteria. The inclusion criteria for the present study were as follows: i) Patients who had undergone NSM or CM; ii) patients aged <35 years; iii) female patients; and iv) patients with TNM stages 0-IIB at initial diagnosis. The exclusion criteria for the present study were as follows: i) Patients who had received preoperative treatment; ii) patients who had not received adjuvant treatment; iii) patients without available pathological data; iv) patients with synchronous bilateral invasive breast cancer or metachronous contralateral breast cancer; and v) patients without follow-up records. A total of 357 patients were included in the present study.

Surgery. Patients who had been found to be contraindicated with BCS by preoperative imaging, including magnetic resonance imaging, ultrasonography and mammography, and those who had explicitly rejected BCS, were eligible for NSM. Patients with possible tumor involvement in the NAC or surrounding skin, according to preoperative imaging, were not eligible for NSM. Based on the results of fine needle biopsies and clinical staging, CM was performed with or without a sentinel lymph node biopsy. Axillary lymph node dissection was routinely performed when metastasis to the sentinel lymph node had occurred. NSM removed the entire mammary gland parenchyma, including the skin overlying superficial tumors, when possible. Patients with a tumor-to-NAC distance <2 cm, nipple discharge or Paget's disease were not eligible for NSM. When performing NSM, in order to confirm that there was no tumor invasion to the NAC borders, frozen sections of the retroareolar tissue were routinely acquired for intraoperative histological diagnosis. The puncture point of the core biopsy was as far from the NAC and as close to the lump as possible. NSM was followed by immediate breast reconstruction with a permanent implant, latissimus dorsi myocutaneous flap (LD), extended LD (ELD), transverse rectus abdominis myocutaneous flap (TRAM) and deep inferior epigastric artery perforator flap (DIEP), which was performed by the same team in a single operative procedure. The reconstructive procedure was selected depending on the anatomical conditions and personal preferences of patients.

Adjuvant therapy. Adjuvant systemic treatment and radiation therapy were administered according to the National Comprehensive Cancer Network guidelines (29) and based on the postoperative pathological examinations. Adjuvant therapy included chemotherapy, endocrine therapy, radiotherapy and targeted therapy. Patients were normatively treated according to the most recent guidelines at the time of treatment.

Statistical analysis. The patient clinicopathological features were compared between the NSM and CM groups using the χ^2 (when the theoretical frequency was >1) or Fisher's exact tests (when the theoretical frequency was <1). The present study was not a randomized controlled trial and statistical differences in certain clinicopathological features, including the clinical TNM stage, of a number of patients were observed between the 2 groups. Therefore, Kaplan-Meier survival analysis, followed by the log-rank test, was used to compare the LR, DFS and OS rates between the two groups; and the clinical TNM stage-stratified log-rank test was also used to compare the LR and DFS rates. The Cox proportional hazards model was used to evaluate the prognostic factors of DFS. All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Cosmetic assessment. The postoperative cosmetic outcome of the patients who had undergone NSM, followed by immediate breast reconstruction, was evaluated by a panel comprising three surgeons and patients, and was stratified into 5 grades (excellent, good, acceptable, poor or very poor). Evaluation was based on 4 criteria, including symmetry of size and shape, symmetry of NAC and inframammary fold, the visibility of scarring and skin color match. Each criterion was evaluated with 0 to 5 points. The total score 17 to 20 was categorized as excellent, 13 to 16 as good, 9 to 12 as acceptable, 5 to 8 as poor and 0 to 4 as very poor.

Ethical approval and informed consent. All procedures in the present study involving human participants were performed in accordance with the ethical standards of Guangxi Medical University Affiliated Tumor Hospital research committee (approval no. 14-06) and with the 1964 Declaration of Helsinki and its later amendments (30). The present study was approved by the Review Board of Guangxi Medical University Affiliated Tumor Hospital and Liuzhou People's Hospital. The study used only unidentifiable patient information and therefore, no written informed consent was required.

Results

Patient characteristics. A total of 357 patients were selected for the present study; of which, 163 patients (45.7%) had undergone NSM and 194 (54.3%) had undergone CM. The patient clinicopathological features are summarized in Table I. Patients who had undergone NSM exhibited a smaller tumor size, a lower proportion of lymph node metastasis and a lower proportion of stage II disease, compared with the CM group. There were no statistical differences in age, histological grade, ER and PR status and HER-2 status between the NSM and CM groups.

Surgery. All patients from the NSM group had undergone breast reconstruction, of which 148 patients (90.8%) had undergone immediate breast reconstruction and 15 patients (9.2%) had undergone delayed breast reconstruction. The reconstruction method included permanent implant (32 cases, 19.6%), LD (51 cases, 31.2%), ELD (59 cases, 36.2%), TRAM (18 cases, 11.0%) and DIEP (3 cases, 1.8%). Only 4 patients in the CM group had undergone delayed breast reconstruction with ELD or a tissue expander followed by a permanent implant. None of the patients in the CM group had undergone immediate breast reconstruction.

Complications. Nipple necrosis occurred in 4 patients (2.5%) who had undergone breast reconstruction with permanent implants, ELD and TRAM. Partial necrosis of breast skin or the myocutaneous flap was observed in 18 patients (11.0%) who had undergone breast reconstruction with permanent implants and TRAM. Complete necrosis of the myocutaneous flap was observed in 1 patient (0.6%) who had undergone breast reconstruction with DIEP. No flap necrosis was observed in the patients that had undergone breast reconstruction with LD or ELD. There were no patients with a hematoma requiring surgical intervention or an infection requiring removal of the implant.

Oncological outcomes. All patients were followed up for a period of 4-118 months, with a median follow-up time of 49 months. The median follow-up time in the NSM and CM groups were 39 months (range, 4-112 months) and 53 months (range, 4-118 months), respectively. In the NSM group, 22 patients (13.5%) experienced recurrence, of which 6 (27.3%) exhibited LR only, 15 (68.2%) exhibited systemic recurrence only and 1 (4.5%) exhibited LR and systemic recurrence. In the CM group, 33 patients (17.0%) experienced recurrence, of which 3 (9.1%) exhibited LR only, 27 (81.8%) exhibited systemic recurrence only and 3 (9.1%) exhibited LR and systemic recurrence.

There were no significant differences in the 5-year LR rate of the NSM and CM groups (4.3 vs. 3.1%; P=0.228; Fig. 1) or in the 5-year DFS rate of the two groups (86.5 vs. 83.0%; P=0.780; Fig. 2). The 5-year OS rates were similar for the two groups (94.5 vs. 92.3%; P=0.868; Fig. 3). Following adjustment for the clinical TNM stage, there were no statistically significant differences in the LR and DFS rates between the two groups (Figs. 4 and 5). In multivariate analysis (Table II), the significant risk factors for DFS following NSM or CM were positive lymph nodes, higher clinical TNM stage, negative ER/PR expression and positive HER-2 expression. The surgical procedure was not a significant risk factor for DFS (HR=1.041; 95% confidence interval=0.585-1.851; P=0.892).

Table I. Comparison of clinical characteristics between the NSM group (n=163) and the CM group (n=194).

	NSM group		CM group		
Characteristic	n	%	n	%	P-value
Age, years					
<30	29	17.8	23	11.9	0.113
30-34	134	82.2	171	88.1	
T stage					
T0	3	1.8	5	2.6	0.047[a]
T1	70	42.9	58	29.9	
T2	90	55.2	129	66.5	
T3	0	0	2	1.0	
Nodal status					
+	54	33.1	89	45.9	0.014[a]
-	109	66.9	105	54.1	
Clinical TNM stage					
0	3	1.8	5	2.6	0.015[a]
I	59	36.2	44	22.7	
IIA	58	35.6	68	35.1	
IIB	43	26.4	77	39.7	
Histological grade					
I	35	21.5	31	16.0	0.357
II	70	42.9	84	43.3	
III	58	35.6	79	40.7	
ER status					
+	111	68.1	116	59.8	0.104
-	52	31.9	78	40.2	
PR status					
+	101	62.0	110	56.7	0.314
-	62	38.0	84	43.3	
HER-2 status					
+	69	42.3	97	50.0	0.148
-	78	47.9	73	37.6	
Unknown	16	9.8	24	12.4	

[a]P<0.05. NSM, nipple-sparing mastectomy; CM, conventional mastectomy; T, tumor; TNM, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

Treatment of LR with NSM. In the NSM group, 7 patients presented with LR. Of these cases, NAC, skin and incision scar recurrences were observed in 2 (1.2%), 4 (2.5%) and 1 case(s) (0.6%), respectively. The local recurrent lesions of the 6 patients with LR only were excised completely. All margins were negative and none of the patients required total

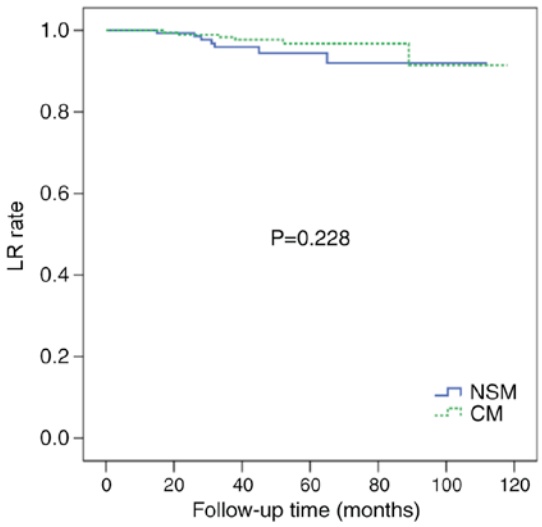

Figure 1. Unadjusted 5-year LR rates of patients who had undergone NSM or CM. LR, local recurrence; NSM, nipple-sparing mastectomy; CM, conventional mastectomy.

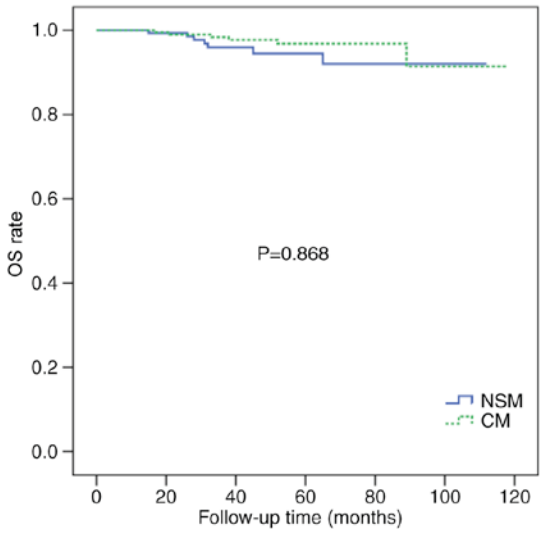

Figure 3. Unadjusted 5-year OS rates of patients who had undergone NSM or CM. OS, overall survival; NSM, nipple-sparing mastectomy; CM, conventional mastectomy.

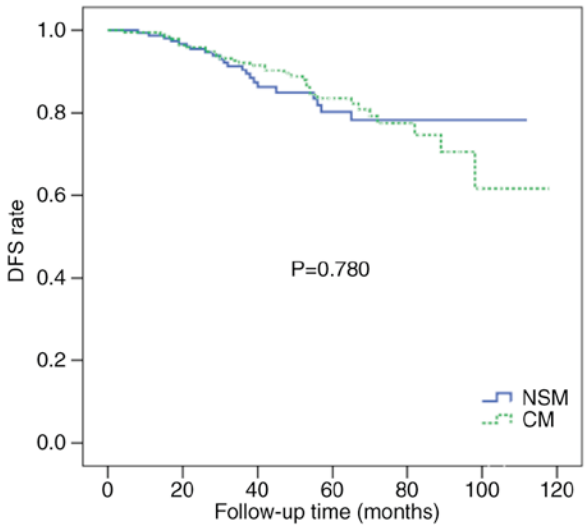

Figure 2. Unadjusted 5-year DFS rates of patients who had undergone NSM or CM. DFS, disease-free survival; NSM, nipple-sparing mastectomy; CM, conventional mastectomy.

mastectomy. All these patients underwent chemotherapy and radiation therapy following surgery. No novel recurrences were observed during follow-up. The patient with LR and systemic recurrence underwent chemotherapy and radiation therapy, but liver failure caused by liver metastasis resulted in mortality 18 months later.

Cosmetic outcome. The postoperative cosmetic outcome evaluated by patients was 'excellent' in 45/163 patients (27.6%), 'good' in 85/163 patients (52.1%), 'acceptable' in 24/163 patients (14.7%), 'poor' in 8/163 patients (4.9%) and 'very poor' in 1/163 patients (0.6%). The postoperative cosmetic outcome evaluated by the panel was 'excellent' in 38/163 patients (23.3%), 'good' in 77/163 patients (47.2%), 'acceptable' in 36/163 patients (22.1%), 'poor' in 11/163 patients (6.7%) and 'very poor' in 1/163 patients (0.6%). There was only one patient who was graded as 'very poor' due to complete necrosis of the DIEP flap. The overall percentage of patients with 'excellent' or 'good' rating was 75.2%.

Discussion

The typical SSM procedure involves removal of the mammary glands and NAC while sparing the skin envelope and the native inframammary fold (6). It has been demonstrated to be a safe procedure that provides good cosmetic results with excellent local tumor control rate (7,8,31). NSM is similar to SSM but it also preserves the NAC. Due to its preservation of the NAC, NSM has been considered to have potentially higher LR risks (11). NSM has been used for breast tumors with peripheral locations and even advanced disease (32).

Numerous previous prospective and retrospective studies, comprising patients with varying sample sizes, inclusion criteria and follow-up durations, have reported an LR rate of 0-24% following NSM (12,16-18,32-34). Although Benediktsson and Perbeck (33) reported a highest LR rate of 24% among these studies, the NAC recurrence rate was 4%. While a study undertaken by Adam *et al* (16) reported no LR in a group comprising 67 patients after 36 months. Shimo *et al* (34) determined an LR rate of 5.8% after 46.8 months (range, 6-158 months) for 425 patients who had undergone NSM and the cumulative LR rate at the NAC was 2.3%. Orzalesi *et al* (35) evaluated the oncological safety of NSM in a large sample size (1,006 cases), and reported an LR rate of 2.9% and a NAC recurrence rate of 0.7%. A meta-analysis of 73 studies (12,358 cases) between 1970 and 2015 assessed the incidence of LR following NSM (19). The mean follow-up time was 38 months (range, 7.4-156 months) and the overall LR rate was 2.38%. In recent years, studies have indicated that NSM was safe for oncology and led to similar LR and OS rates compared with those of patients treated with CM (18,34). These results were similar to those of the present study. In the present study, LR was observed in 7 patients (4.3%) in the NSM group, including 2 NAC recurrences (1.2%), and no significant difference was

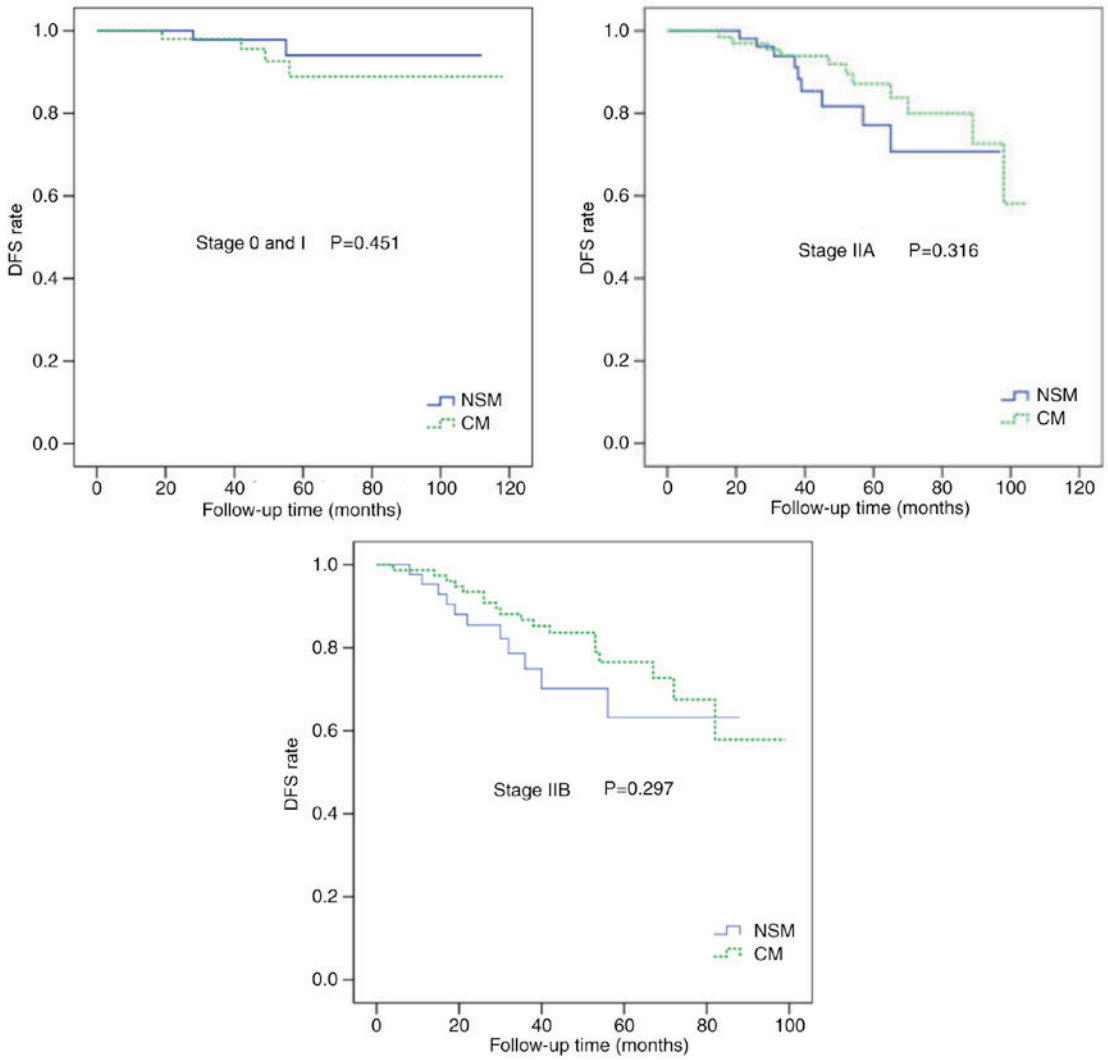

Figure 4. Clinical TNM stage-adjusted 5-year DFS rates of patients who had undergone NSM or CM. P-values were calculated using the stratified log-rank test. TNM, tumor-node-metastasis; DFS, disease-free survival; NSM, nipple-sparing mastectomy; CM, conventional mastectomy.

observed in the 5-year LR rate between the NSM and CM groups (4.3 vs. 3.1%; P=0.228).

A number of previous studies have specialized in the oncological safety of young patients who have undergone NSM. In previous studies, the tumors observed in young patients have frequently exhibited a high histological grade, ER/PR negative status, HER-2 positive status, multifocal or multicenter presentation, high proliferation and lymphovascular invasion (23-25,36-39). The presence of these characteristics in young patients with breast cancer has generally been associated with a poorer prognosis (20,21). Fredholm *et al* (22) conducted a population-based study comprising 22,017 female patients with breast cancer and revealed that young age was a risk factor for loco-regional recurrence. In the present study, it was determined that young age did not increase the oncological risk for the female patients with early-stage breast cancer who had undergone NSM. There were no significant statistical differences in the 5-year LR, DFS and OS rates between the NSM and CM groups (Figs. 1-3).

In the present study, patients who had undergone CM exhibited a larger tumor size, a higher proportion of positive lymph nodes and a higher proportion of stage II disease, compared with those who had undergone NSM. There may have been a selection bias towards patients and the patients with early-stage cancer may have been offered NSM more frequently. Patients with a larger tumor size and positive lymph nodes exhibited a higher clinical TNM stage more frequently. In order to reduce the selection bias, analysis was adjusted for clinical TNM stage. It was determined that there were no significant statistical differences in the LR and DFS rates between the two groups when adjusted for clinical TNM stage (Figs. 4 and 5).

Benediktsson and Perbeck reported that LR was dependent on the lymph node status and clinical TNM stage (33). Petit *et al* (40) determined that the number of positive lymph nodes, histological type and Ki-67 index were significant predictive factors of LR based on multivariate analysis. Due to the limited number of LR cases, the prognostic factors of LR based on multivariate analysis could not be evaluated. However, it was revealed that the significant risk factors for DFS following NSM or CM were positive lymph nodes, negative ER/PR expression and positive HER-2 expression.

In addition to oncological safety, complication rates and cosmetic outcome are two other concerns associated with

Table II. Multivariate analysis of clinical characteristics and prognosis in young females treated with NSM or CM.

							95% CI	
Clinical characteristic	B	SE	Wald	d.f.	P-value	Exp(B)	Lower limit	Upper limit
Surgical procedure	0.040	0.294	0.018	1	0.892	1.041	0.585	1.851
Age	-0.031	0.057	0.301	1	0.583	0.969	0.867	1.084
Tumor size	-0.301	0.334	0.812	1	0.368	0.740	0.384	1.425
Nodal status	1.229	0.541	5.172	1	0.023[a]	3.419	1.185	9.865
Clinical TNM stage	0.984	0.395	6.212	1	0.013[a]	2.676	1.234	5.803
Histological grade	-0.083	0.195	0.179	1	0.672	0.921	0.628	1.349
ER status	-0.944	0.290	10.592	1	0.001[a]	0.389	0.220	0.687
PR status	-1.234	0.306	16.302	1	0.006[a]	0.291	0.160	0.530
HER-2 status	-0.562	0.241	5.415	1	0.020[a]	0.570	0.355	0.915

[a]P<0.05. Surgical procedures included NSM and CM.B, B coefficient; SE, standard error; d.f., degrees of freedom; Exp(B), exponentiation of the B coefficient; CI, confidence interval; TMN, tumor-node-metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

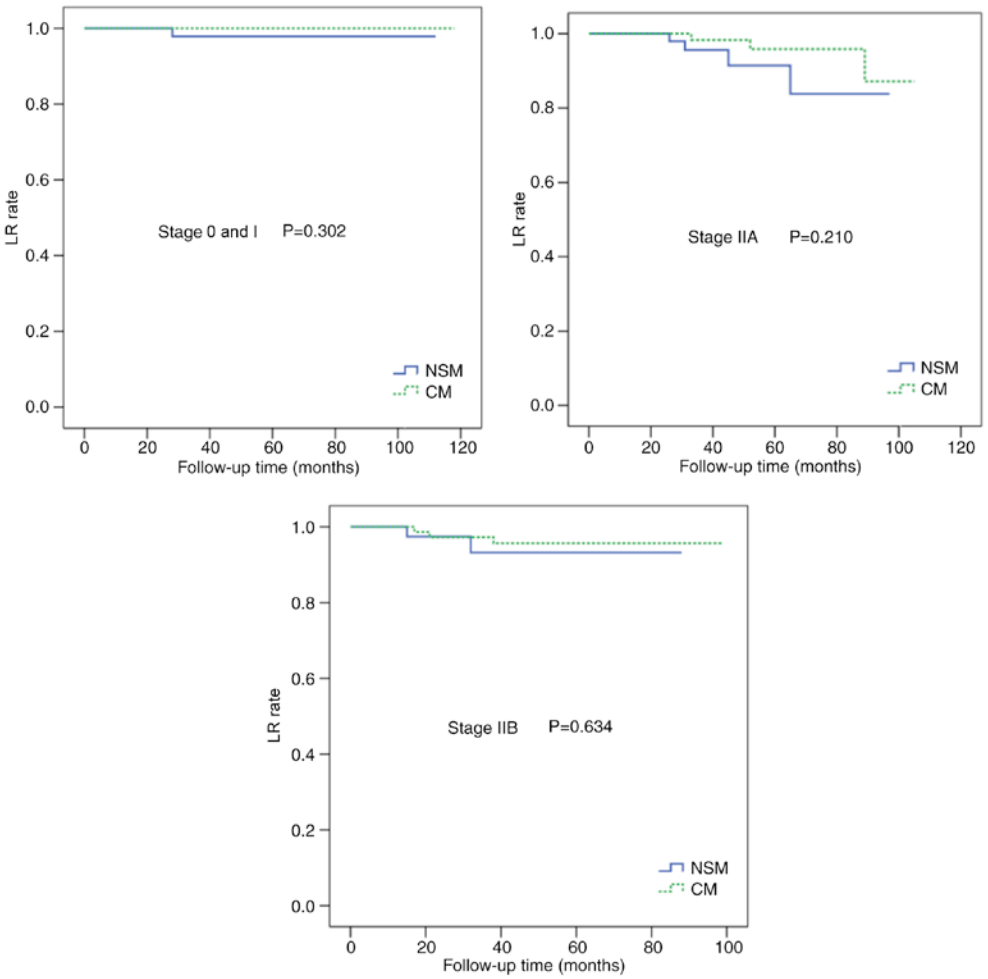

Figure 5. Clinical TNM stage-adjusted LR rates in patients undergoing NSM or CM. P-values were calculated using the stratified log-rank test. TNM, tumor-node-metastasis; LR, local recurrence; NSM, nipple-sparing mastectomy; CM, conventional mastectomy.

NSM. Due to the removal of the tissue beneath the NAC, NSM may cause an increased incidence of NAC necrosis. Headon *et al* (19) analyzed 73 studies in their meta-analysis and determined a nipple necrosis rate of 5.8% for 12,358 NSM procedures. In the present study, nipple necrosis occurred in 4 patients (2.5%), less than the result reported

by Headon *et al* (19). Arteriosclerosis rarely occurs in young female patients and the majority of patients in the present study were non-smokers, which may be a reason for the low nipple necrosis rate observed. Furthermore, avoiding the use of high frequency electrotomes when removing the tissue beneath the NAC (41) and maintaining the thickness of the areola flap under the premise of oncological safety are also important for reducing nipple areola necrosis (42). One advantage of the NSM procedure, the cosmetic outcome, has been recognized by the majority of experts (43,44). Yueh *et al* (44) reported that the NSM procedure provided patients with a superior cosmetic outcome and psychological satisfaction. The majority of the patients that had undergone NSM followed by breast reconstruction in the present study obtained a satisfactory cosmetic appearance. The overall rates of 'excellent' and 'good' grades averaged 75.2%. A positive body image is particularly important for these young female patients with breast cancer. Physical defects in young women can lead to poorer mental health, lower self-esteem and sexual dysfunction, thereby significantly affecting their quality of life (45).

There were certain limitations associated with the present study. To begin with, the present study was retrospective and only comprised a small number of patients (357 cases), thereby resulting in unavoidable bias. In particular, the tendency to perform NSM on patients with early-stage cancer led to a selection bias. Secondly, the median follow-up time of the present study was 49 months (39 months for the NSM group and 53 months for the CM group), which was relatively short, compared with the long natural course of breast cancer. The present study only included patients <35 years of age. A longer follow-up is required to demonstrate the natural course of breast cancer in these young patients. Furthermore, the clinical TNM stages of patients in the present study were between stage 0 and IIB, but these patients exhibited a relatively high proportion of recurrence and mortality. A considerable proportion of HER-2 positive patients may not have received Herceptin® therapy due to financial reasons, which posed a notable social problem.

In summary, compared with CM, NSM did not increase the risk of local and systemic recurrence in young patients with early-stage breast cancer in the present study. The NSM procedure achieved oncological safety and superior cosmetic outcomes for the young females with breast cancer. Therefore, NSM may become one of the standard procedures for the young patients with early-stage breast cancer when breast reconstruction is performed.

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Competing interests

The authors declare that they have no competing interests.

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