

Oncological Outcomes of Skin-Sparing and Nipple-Sparing Mastectomy After Neoadjuvant Chemotherapy: A Prospective Single-Institution Cohort Study

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ABSTRACT

Background: Skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) facilitate immediate breast reconstruction but remain oncologically controversial after neoadjuvant chemotherapy (NACT), particularly in locally advanced breast cancer. This study compared short-term oncological and postoperative outcomes of SSM/NSM with modified radical mastectomy (MRM) after NACT. **Methods:** This prospective cohort included 200 women aged 18–65 years at the National Cancer Institute, Cairo University. Following multidisciplinary assessment, 100 underwent SSM/NSM with immediate reconstruction and 100 underwent MRM. Preoperative response assessment used mammography, ultrasonography, and magnetic resonance or contrast-enhanced imaging when indicated. Margins, including the retroareolar margin when applicable, were assessed intraoperatively and confirmed histologically. Patients were followed for 24 months. Survival was evaluated using Kaplan–Meier analysis, restricted mean survival time, multivariable Cox regression, and inverse probability of treatment weighting. **Results:** Baseline clinicopathological, molecular, and pathological-response characteristics were comparable. All surgical margins were negative. Hospital stay was longer after SSM/NSM than MRM (5.41 ± 1.99 vs 1.89 ± 0.85 days; $P < 0.001$), and skin necrosis was more frequent (10.0% vs 2.0%; $P = 0.033$); hematoma, seroma, surgical-site infection, and Clavien–Dindo grades did not differ significantly. Among patients completing follow-up, local recurrence occurred in 8.7% versus 3.2% ($P = 0.130$). At 24 months, disease-free survival was 88.9% versus 93.0%, overall survival 99.0% versus 98.0%, distant metastasis-free survival 99.0% versus 98.0%, and local recurrence-free survival 92.0% versus 97.0%; none differed significantly. Adjusted and weighted analyses were consistent. **Conclusion:** Carefully selected patients undergoing SSM/NSM after NACT had oncological outcomes comparable with MRM, but experienced more skin necrosis and longer hospitalization. Longer follow-up and separate evaluation of SSM and NSM are required.

Keywords: breast cancer; neoadjuvant chemotherapy; nipple-sparing mastectomy; skin-sparing mastectomy; modified radical mastectomy; recurrence; reconstruction.

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INTRODUCTION

Breast cancer surgery has progressively moved from maximally extensive operations toward procedures that preserve form and facilitate reconstruction without compromising disease control. Skin-sparing mastectomy (SSM) removes the breast parenchyma and nipple–areola complex (NAC) while preserving most of the skin envelope, whereas nipple-sparing mastectomy (NSM) additionally preserves the NAC. Both approaches can improve breast contour, body image, and reconstructive outcomes compared with conventional mastectomy, although NSM may provide additional psychosocial and aesthetic benefit [1,2].

Neoadjuvant chemotherapy (NACT) is integral to the multidisciplinary treatment of locally advanced breast cancer because it can downstage the breast and axilla, provide information about treatment response, and facilitate definitive surgery. Nevertheless, the extension of SSM and NSM to patients treated with NACT remains controversial.

Residual microscopic disease may persist within preserved skin flaps or retroareolar tissue, and the available evidence is dominated by observational studies with heterogeneous selection criteria, reconstructive techniques, systemic regimens, and follow-up periods [3,4].

Careful patient selection and reliable assessment of NAC involvement are therefore essential. Clinical examination, post-NACT imaging, tumor-to-nipple distance, and pathological examination of retroareolar tissue are commonly used to reduce the risk of occult nipple involvement. Clinicopathological series have identified tumor location, tumor size, nodal disease, and short tumor-to-nipple distance as potential predictors of NAC involvement, although contemporary practice has gradually expanded beyond rigid distance thresholds when imaging and margin assessment are reassuring [5,6].

Envelope-preserving surgery also introduces a distinct morbidity profile. Longer and thinner mastectomy flaps, preservation of the NAC, and immediate reconstruction

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may increase ischemic complications, including skin-flap and nipple necrosis. These events can compromise reconstruction, require reoperation, prolong hospitalization, and delay adjuvant treatment. Accordingly, the present prospective cohort study compared SSM/NSM with MRM after NACT in women with advanced breast cancer. The objectives were to evaluate margin safety, postoperative morbidity, recurrence patterns, and 24-month oncological outcomes, while accounting for confounding inherent in non-randomized surgical selection.

PATIENTS AND METHODS

Study design and setting

This prospective observational cohort study was conducted in the Department of Surgical Oncology, National Cancer Institute, Cairo University. Patients were evaluated by a multidisciplinary tumor board before surgery and were assigned to SSM/NSM or MRM according to oncological suitability, breast anatomy, reconstructive candidacy, and patient preference. Because treatment allocation was not randomized, the analysis incorporated multivariable and propensity-score methods to address measured confounding.

Participants

Eligible participants were women aged 18–65 years with World Health Organization performance status 0–1 and advanced breast cancer requiring mastectomy after NACT. The source thesis specified clinical presentations including T2N1, T3N0, and T3N1 disease, as well as selected unifocal or multifocal tumors with a very good response to NACT when the initial disease site could not be reliably localized for breast-conserving surgery.

Exclusion criteria were T4 disease at presentation, distant metastasis developing during treatment, previous ipsilateral breast cancer, documented progression during NACT, clinical or imaging contraindication to nipple preservation (including a skin-to-nipple distance <10 mm as stated in the thesis), and contraindications to immediate reconstruction such as uncontrolled diabetes or active smoking at surgery.

Sample size calculation

The sample size was based on previously reported local recurrence rates of 11.0% after NSM/SSM and 4.7% after MRM [8]. Assuming a between-group difference of 6.3%, 80% power, and a two-sided significance level of 5%, 168 patients (84 per group) were required. Allowing for 15% attrition increased the target to 194 patients (97 per group). The final cohort included 200 participants, with 100 in each surgical group. The source thesis did not specify the software used for this calculation.

Clinical assessment and imaging

Baseline assessment included demographic, reproductive, family, medical, and treatment history; body mass index; World Health Organization performance status; and comprehensive breast, axillary, and systemic examination. Digital mammography documented residual calcifications and architectural distortion, ultrasonography assessed tumor extent and axillary nodes, and breast magnetic resonance imaging was used when clinically indicated, particularly for dense breasts, suspected multifocal or multicentric disease, and evaluation of the NAC. Metastatic staging included computed tomography of the chest,

abdomen, and pelvis and bone scintigraphy, with positron-emission tomography/computed tomography used when recommended by the multidisciplinary team.

Response to NACT was assessed within two weeks of the final chemotherapy cycle using contrast-enhanced spectral mammography or breast magnetic resonance imaging. Residual disease, shrinkage pattern, and possible NAC involvement were documented according to RECIST version 1.1. Standard laboratory and cardiopulmonary assessments were performed to determine anaesthetic fitness.

Surgical procedures and pathological assessment

Patients underwent SSM or NSM with immediate reconstruction, or MRM as the comparison procedure. Incisions for envelope-preserving surgery included inframammary, periareolar, and lateral radial approaches, selected according to breast size, tumor location, and reconstructive requirements. Reconstruction was implant-based or autologous, including latissimus dorsi, transverse rectus abdominis myocutaneous, or deep inferior epigastric perforator flaps. Sentinel lymph-node biopsy was performed in clinically and radiologically node-negative axillae, whereas axillary lymph-node dissection was undertaken for proven nodal disease or intraoperative nodal positivity.

Surgical margins and, when applicable, the retroareolar margin were examined intraoperatively by frozen section and were confirmed on permanent histopathology. Pathological tumor type, grade, hormone-receptor status, HER2 status, Ki-67, lymphovascular invasion, and pathological response were recorded. Response to NACT was categorized using the Chevallier classification.

Outcomes and follow-up

The principal oncological outcomes were negative resection margins, local recurrence, disease-free survival (DFS), overall survival (OS), distant metastasis-free survival (DMFS), and local recurrence-free survival (LRFS). Postoperative outcomes included length of hospital stay, hematoma, seroma, surgical-site infection, skin or NAC necrosis, and complication severity according to the Clavien–Dindo classification. Skin or NAC necrosis was defined as partial or complete loss of tissue viability requiring additional wound care, debridement, grafting, or another intervention.

Follow-up visits occurred every two months during the first postoperative year and every three months during the second year. Each visit included clinical evaluation for wound complications and recurrence, with ultrasonography, mammography, magnetic resonance imaging, or metastatic investigations obtained as clinically indicated. Time-to-event follow-up was capped at 24 months.

Ethical considerations

The protocol was approved by the Ethics Committee of the National Cancer Institute, Cairo University (MD-21-2021). All participants provided written informed consent. Records and specimens were anonymized, participation was voluntary, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was investigator funded and received no external financial support.

Statistical analysis

Analyses were reported as performed in the source thesis using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA). Distributional assumptions were assessed with the Kolmogorov–Smirnov test. Continuous variables were summarized as mean±standard deviation or median (interquartile range), and categorical variables as number and percentage. Independent-samples t tests or Mann–Whitney U tests were used for continuous variables, and chi-square or Fisher exact tests for categorical variables. Procedural variables intrinsically determined by the surgical approach, such as incision and reconstruction type, were described without significance testing.

DFS, OS, DMFS, and LRFS were measured from surgery to the relevant event or last follow-up and were analyzed using Kaplan–Meier methods. Survival probabilities at 12 and 24 months were compared by the log-rank test; median survival was not reported because it was not reached. Restricted mean survival time (RMST) to 24 months was calculated as a complementary absolute measure, with 95% confidence intervals obtained from 2,000 bootstrap resamples.

Multivariable Cox proportional-hazards models estimated the association of surgical group with survival outcomes after adjustment for prespecified prognostic factors, including clinical stage, nodal status, lymphovascular invasion, and intrinsic tumor subtype. Reduced models were used for endpoints with few events to limit overfitting. Results are presented as hazard ratios (HRs) with 95% confidence intervals.

As a sensitivity analysis, a propensity score for MRM versus SSM/NSM was estimated by logistic regression using age, body mass index, clinical T and N categories, clinical stage, intrinsic subtype risk, tumor-to-NAC distance, and core-biopsy grade. Stabilized inverse probability of treatment weights estimated the average treatment effect. Balance was evaluated using standardized mean differences (SMDs), with SMD <0.10 considered acceptable. Weighted Cox models estimated marginal group effects. Tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Study population and baseline characteristics

The cohort comprised 200 women with advanced breast cancer treated with NACT and subsequent mastectomy: 100 underwent SSM/NSM with immediate reconstruction and 100 underwent MRM. Age, body mass index, menopausal status, parity, breastfeeding and hormonal-contraception histories, and family cancer history did not differ significantly between groups (Table 1).

Baseline tumor characteristics were also broadly comparable. There were no statistically significant differences in breast side, tumor quadrant, clinical T or N category, focality, core-biopsy grade, intrinsic molecular

subtype, ER, PR, HER2, Ki-67, or histological tumor type (Table 2).

Surgical and pathological findings

Procedural characteristics differed by design (Table 3). Inframammary, periareolar, or lateral radial incisions were used for SSM/NSM, whereas MRM used elliptical variants. Every patient in the SSM/NSM group underwent immediate reconstruction: 67% received an autologous flap and 33% implant-based reconstruction. No MRM patient underwent immediate reconstruction. All final resection margins were negative. These procedural variables were not statistically compared because they were intrinsic components of the assigned surgical pathway.

Pathological response after NACT was similar between groups. Chevallier class IV was observed in 72% after SSM/NSM and 70% after MRM, while lymphovascular invasion was present in 19% and 29%, respectively; neither difference was significant (Table 4).

Postoperative morbidity

SSM/NSM was associated with a longer hospital stay than MRM (mean, 5.41 ± 1.99 vs 1.89 ± 0.85 days; median, 5 vs 2 days; $P < 0.00001$). Skin necrosis occurred in 10 patients (10.0%) after SSM/NSM and two patients (2.0%) after MRM ($P = 0.033$). Hematoma, seroma, surgical-site infection, and the distribution of Clavien–Dindo complication grades were not significantly different (Table 5).

Recurrence and survival

Follow-up to the planned endpoint was completed by 92 patients in the SSM/NSM group and 94 in the MRM group. Among these patients, local recurrence occurred in 8.7% and 3.2%, respectively ($P = 0.130$). Three local recurrences involved the NAC in the SSM/NSM group; no NAC recurrence was possible in the MRM group. Regional recurrence and distant metastasis were uncommon and did not differ significantly (Table 6).

Kaplan–Meier analysis showed no significant difference in any time-to-event endpoint (Table 7). At 24 months, DFS was 88.9% after SSM/NSM and 93.0% after MRM (log-rank $P = 0.31$); OS was 99.0% and 98.0% ($P = 0.56$); DMFS was 99.0% and 98.0% ($P = 0.32$); and LRFS was 92.0% and 97.0% ($P = 0.12$). RMST differences through 24 months were small and non-significant for DFS, DMFS, and LRFS. In multivariable Cox models, MRM versus SSM/NSM was not independently associated with DFS (adjusted HR, 0.55; 95% CI, 0.23–1.34), OS (adjusted HR, 4.35; 95% CI, 0.30–63.17), DMFS (adjusted HR, 1.72; 95% CI, 0.15–19.34), or LRFS (adjusted HR, 0.35; 95% CI, 0.09–1.32) (Table 8). Propensity weighting achieved excellent balance (maximum post-weighting SMD, 0.018; maximum stabilized weight, 2.19). IPTW-weighted estimates were consistent with the unadjusted and multivariable analyses and showed no significant association between surgical approach and DFS, DMFS, or LRFS.

Table 1. Baseline demographic and reproductive characteristics

Characteristic	SSM/NSM (n=100)	MRM (n=100)	P value
Age, years, mean±SD	46.49±11.38	47.59±12.20	0.468
Body mass index, kg/m ² , mean±SD	27.51±2.36	27.87±2.39	0.226
BMI category, n (%)			0.562
≤24.9 kg/m ²	17 (17.0)	13 (13.0)	
25.0–29.9 kg/m ²	65 (65.0)	64 (64.0)	
≥30.0 kg/m ²	18 (18.0)	23 (23.0)	
Menopausal status, n (%)			0.292
Premenopausal	30 (30.0)	30 (30.0)	
Perimenopausal	22 (22.0)	31 (31.0)	
Postmenopausal	48 (48.0)	39 (39.0)	
Parity, mean±SD	3.00±1.78	2.63±1.57	0.156
Previous breastfeeding, n (%)	73 (73.0)	69 (69.0)	0.640
Previous oral contraceptive use, n (%)	26 (26.0)	25 (25.0)	0.908
Any family history of breast/ovarian/endometrial cancer, n (%)	15 (15.0)	17 (17.0)	0.599

Data are mean±SD or n (%). BMI, body mass index; MRM, modified radical mastectomy; NSM, nipple-sparing mastectomy; SSM, skin-sparing mastectomy. P values were derived using the independent-samples t test, Mann–Whitney U test, chi-square test, or Fisher exact test as appropriate.

Table 2. Baseline tumor and clinicopathological characteristics

Characteristic	SSM/NSM (n=100)	MRM (n=100)	P value
Tumor side, n (%)			0.143
Left	68 (68.0)	57 (57.0)	
Right	32 (32.0)	43 (43.0)	
Clinical T category, n (%)			0.549
T2	64 (64.0)	69 (69.0)	
T3	36 (36.0)	31 (31.0)	
Clinical N category, n (%)			0.599
N1	61 (61.0)	54 (54.0)	
N2	24 (24.0)	29 (29.0)	
N3	15 (15.0)	17 (17.0)	
Tumor focality, n (%)			0.296
Unifocal	70 (70.0)	62 (62.0)	
Multifocal	30 (30.0)	38 (38.0)	
Core-biopsy grade, n (%)			0.089
Grade 1	25 (25.0)	19 (19.0)	
Grade 2	54 (54.0)	42 (42.0)	
Grade 3	21 (21.0)	39 (39.0)	
Intrinsic subtype, n (%)			0.923
Luminal A	35 (35.0)	33 (33.0)	
Luminal B	33 (33.0)	31 (31.0)	
HER2-positive	12 (12.0)	15 (15.0)	
Triple-negative	20 (20.0)	21 (21.0)	
ER-positive, n (%)	78 (78.0)	76 (76.0)	0.866
PR-positive, n (%)	72 (72.0)	65 (65.0)	0.361
HER2-positive, n (%)	12 (12.0)	15 (15.0)	0.679
High Ki-67 (≥20%), n (%)	64 (64.0)	67 (67.0)	0.766
Histological type, n (%)			0.405
Invasive ductal carcinoma	78 (78.0)	69 (69.0)	
Invasive lobular carcinoma	17 (17.0)	26 (26.0)	
Mixed carcinoma	3 (3.0)	4 (4.0)	
Other	2 (2.0)	1 (1.0)	

Data are n (%). ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor. Exact or chi-square tests were used as appropriate.

Table 3. Surgical approach, reconstruction, and margin status

Characteristic	SSM/NSM (n=100)	MRM (n=100)	P value
Incision type			Not tested
Inframammary fold	48 (48.0)	0	
Lateral radial	13 (13.0)	0	
Periareolar	39 (39.0)	0	
Elliptical (Stewart)	0	64 (64.0)	
Extended elliptical	0	6 (6.0)	
Modified elliptical	0	30 (30.0)	
Reconstruction type			Not tested
Autologous flap	67 (67.0)	0	
Implant-based	33 (33.0)	0	
None or delayed	0	100 (100.0)	
Negative final resection margin	100 (100.0)	100 (100.0)	Not applicable

Data are n (%). Incision and reconstruction variables were not statistically tested because they were structurally determined by the surgical pathway. Final margin status was negative in all patients.

Table 4. Pathological response to neoadjuvant chemotherapy and lymphovascular invasion

Pathological characteristic	SSM/NSM (n=100)	MRM (n=100)	P value
Chevallier response class, n (%)			0.876
Class III	28 (28.0)	30 (30.0)	
Class IV	72 (72.0)	70 (70.0)	
Lymphovascular invasion, n (%)			0.135
Present	19 (19.0)	29 (29.0)	
Absent	81 (81.0)	71 (71.0)	

Data are n (%). Fisher exact tests were used.

Table 5. Postoperative outcomes and complications

Outcome	SSM/NSM (n=100)	MRM (n=100)	P value
Hospital stay, days			<0.00001
Mean±SD	5.41±1.99	1.89±0.85	
Median (IQR)	5 (4–6)	2 (1–3)	
Hematoma, n (%)	6 (6.0)	8 (8.0)	0.782
Seroma, n (%)	13 (13.0)	7 (7.0)	0.238
Surgical-site infection, n (%)	6 (6.0)	12 (12.0)	0.215
Skin necrosis, n (%)	10 (10.0)	2 (2.0)	0.033
Clavien–Dindo grade, n (%)			0.861
I	81 (81.0)	77 (77.0)	
II	9 (9.0)	10 (10.0)	
IIIa	6 (6.0)	6 (6.0)	
IIIb	3 (3.0)	4 (4.0)	
IV	1 (1.0)	3 (3.0)	

Data are mean±SD, median (IQR), or n (%). Hospital stay was compared using the Mann–Whitney U test; binary outcomes used Fisher exact tests; Clavien–Dindo grades used the chi-square test.

Table 6. Follow-up completion and recurrence outcomes

Outcome	SSM/NSM	MRM	P value
Completed 24-month follow-up, n (%)	92 (92.0)	94 (94.0)	0.782
Local recurrence among completers, n (%)	8/92 (8.7)	3/94 (3.2)	0.130
Local recurrence site, n (% of completers)			0.233
Axillary tail	2 (2.17)	1 (1.06)	
Chest wall/skin flap	2 (2.17)	0	
Mastectomy scar	1 (1.08)	2 (2.12)	
Nipple–areola complex	3 (3.26)	0	
Regional recurrence, n (% of completers)	2 (2.17)	2 (2.12)	0.985
Distant metastasis, n (% of completers)	1 (1.08)	2 (2.12)	0.983

Denominators for recurrence outcomes were the patients who completed follow-up (92 SSM/NSM and 94 MRM). Fisher exact or chi-square tests were used as appropriate.

Table 7. Unadjusted time-to-event outcomes and restricted mean survival time

Endpoint	Group	Events	12-month survival, % (95% CI)	24-month survival, % (95% CI)	Log-rank P
Panel A. Kaplan–Meier estimates					
DFS	SSM/NSM	11	96.8 (91.0–98.9)	88.9 (80.9–93.7)	0.31
DFS	MRM	7	97.9 (92.8–99.4)	93.0 (85.9–96.6)	
OS	SSM/NSM	1	100.0	99.0 (93.2–99.9)	0.56
OS	MRM	2	100.0	98.0 (92.3–99.5)	
DMFS	SSM/NSM	1	100.0	99.0 (93.2–99.9)	0.32
DMFS	MRM	2	99.0 (96.0–99.8)	98.0 (92.3–99.5)	
LRFS	SSM/NSM	8	96.8 (91.0–98.9)	92.0 (84.6–95.9)	0.12
LRFS	MRM	3	98.5 (95.4–99.5)	97.0 (91.0–99.0)	
Panel B. RMST through 24 months					
Endpoint	SSM/NSM RMST, months (95% CI)	MRM RMST, months (95% CI)	MRM–SSM/NSM difference, months (95% CI)		P value
DFS	22.63 (21.80–23.37)	23.15 (22.47–23.69)	0.52 (–0.44 to 1.51)		0.299
LRFS	23.22 (22.57–23.75)	23.78 (23.44–24.00)	0.56 (–0.08 to 1.27)		0.080
DMFS	23.86 (23.57–24.00)	23.73 (23.31–24.00)	–0.13 (–0.63 to 0.30)		0.701

DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival; RMST, restricted mean survival time. RMST confidence intervals were derived from 2,000 bootstrap resamples. Median survival was not reached.

Table 8. Adjusted and propensity-weighted survival analyses

Endpoint	Events	Model/covariates	HR (95% CI)	P value
Panel A. Multivariable Cox regression (MRM vs SSM/NSM)				
DFS	21	Clinical stage, nodal status, lymphovascular invasion, intrinsic subtype	0.55 (0.23–1.34)	0.188
DMFS	3	Reduced model: clinical stage, grouped nodal status, grouped subtype	1.72 (0.15–19.34)	0.659
LRFS	11	Reduced model: clinical stage, grouped nodal status, grouped subtype	0.35 (0.09–1.32)	0.120
OS	3	Reduced model: clinical stage, nodal status, intrinsic subtype	4.35 (0.30–63.17)	0.282
Panel B. IPTW-weighted Cox regression (MRM vs SSM/NSM)				
DFS	21	Group effect after weighting	0.74 (0.31–1.75)	0.488
DMFS	3	Group effect after weighting	2.04 (0.19–22.52)	0.560
LRFS	11	Group effect after weighting	0.37 (0.10–1.39)	0.139

HRs >1 indicate higher hazard for MRM relative to SSM/NSM. The propensity model included age, body mass index, clinical T and N categories, clinical stage, intrinsic subtype risk, tumor-to-NAC distance, and core-biopsy grade. Stabilized weights had mean 1.00 and maximum 2.19; the maximum post-weighting standardized mean difference was 0.01

DISCUSSION

In this prospective single-institution cohort, SSM/NSM after NACT was not associated with statistically different short-term DFS, OS, DMFS, or LRFS compared with MRM. This conclusion was consistent across Kaplan–Meier estimates, RMST, multivariable Cox regression, and IPTW-weighted models. However, envelope-preserving surgery with immediate reconstruction was associated with substantially longer hospitalization and a higher incidence of skin necrosis. Local and NAC recurrences were

numerically more frequent after SSM/NSM, but the differences were not statistically significant and were based on small event counts.

These survival findings are consistent with comparative evidence in the post-NACT setting. Wu et al. reported similar long-term oncological outcomes between immediate reconstruction after SSM/NSM and conventional mastectomy after propensity-score matching [7]. In a related analysis focusing on NSM after NACT, no clear survival disadvantage was demonstrated when patients were carefully selected [8]. A matched long-term cohort published by Shin et al. likewise found no significant differences in locoregional recurrence-free survival, DFS, DMFS, or OS between immediate reconstruction after SSM/NSM and total mastectomy alone [10]. Together with systematic reviews, these studies support the oncological feasibility of envelope-preserving mastectomy after NACT, while not establishing formal equivalence in the absence of

randomized or adequately powered non-inferiority designs [3,4].

Local recurrence warrants particular attention because preserved skin and retroareolar structures may contain residual glandular or malignant tissue. The present cohort recorded local recurrence in 8.7% of evaluable SSM/NSM patients compared with 3.2% after MRM. Three events involved the NAC. Wu et al. reported a five-year cumulative locoregional recurrence rate of approximately 11% and identified post-NACT Ki-67, tumor grade, and lymphovascular invasion as important predictors, emphasizing the influence of tumor biology [9]. The current NAC event proportion appears higher than many published NSM series, including the large single-center experience reported by Galimberti et al. [11] and the pooled evidence summarized by Zaborowski et al. [3]. However, direct comparison is limited by the advanced post-NACT case mix, differences in denominator and follow-up, and the very small number of events. The findings therefore support continued surveillance rather than a definitive conclusion of equal local control.

The absence of positive final margins in either group supports the study's selection and intraoperative assessment strategy. The oncological safety of NSM depends on complete glandular excision and reliable exclusion of NAC involvement. Histopathological studies have shown that occult nipple involvement is associated with clinicopathological factors such as tumor size, location, nodal status, and tumor-to-nipple distance [5,6]. In the present study, post-NACT imaging was combined with frozen-section assessment of surgical and retroareolar margins, an approach aligned with the principle that NAC preservation should be abandoned when margin safety is uncertain.

The main morbidity signal was skin necrosis, which occurred in 10% after SSM/NSM versus 2% after MRM. Mastectomy-flap necrosis is influenced by patient comorbidity, smoking, breast size and ptosis, incision choice, flap thickness, perfusion, and reconstructive tension, and it may require debridement, threaten an implant or flap, and delay adjuvant therapy [12]. The longer hospital stay after SSM/NSM should also be interpreted in light of the reconstructive pathway: all women in this group underwent immediate reconstruction, whereas no MRM patient did. Thus, the observed difference cannot be attributed solely to preservation of the skin or nipple. A systematic review by Varghese et al. did not identify a uniform increase in immediate-reconstruction complications after NACT [13], while Bartholomew et al. highlighted the importance of timing, patient selection, and short-term complications in NSM following NACT [14].

The complementary statistical methods strengthen interpretation. RMST supplied an absolute time-based comparison when medians were not reached and event counts were low. Multivariable Cox regression addressed established prognostic factors, and IPTW reduced measured baseline imbalance to a maximum SMD of 0.018. The agreement of these methods reduces the likelihood that the principal survival findings arose solely from observed covariate imbalance. Nevertheless, wide confidence

intervals, particularly for OS and DMFS, show that clinically important differences cannot be excluded.

STRENGTHS AND LIMITATIONS

Strengths include the prospective cohort design, multidisciplinary selection, standardized post-NACT imaging and margin assessment, balanced baseline clinicopathological characteristics, structured two-year follow-up, anatomical documentation of recurrence, and the use of unadjusted, adjusted, RMST, and propensity-weighted analyses. The study also reports the reconstructive pathway and clinically relevant ischemic complications rather than focusing only on recurrence.

Several limitations should temper interpretation. First, treatment was not randomized, so residual confounding by anatomy, surgeon judgment, patient preference, and unmeasured prognostic factors remains possible despite IPTW. Second, this was a single-center study, limiting generalizability. Third, follow-up was restricted to 24 months and the numbers of deaths, distant metastases, and local recurrences were small, leading to imprecise estimates and inadequate assessment of late events. Fourth, SSM and NSM were combined, preventing separate evaluation of NAC preservation. Fifth, immediate reconstruction was completely associated with the SSM/NSM pathway and absent after MRM; consequently, differences in hospitalization and necrosis reflect the entire treatment pathway rather than mastectomy type alone. Sixth, patient-reported aesthetic satisfaction and body image, although mentioned among the thesis objectives, were not reported in the available results. Finally, comparative details regarding NACT regimens, radiotherapy, adjuvant systemic treatment, surgeon-specific technique, and reconstruction-related failure were not incorporated into the principal outcome tables.

CONCLUSION

In carefully selected women with advanced breast cancer treated with NACT, SSM/NSM with immediate reconstruction produced 24-month oncological outcomes that were not statistically different from those after MRM. Margin assessment was satisfactory, and adjusted and propensity-weighted analyses did not identify surgical approach as an independent predictor of DFS, OS, DMFS, or LRFS. These findings support the short-term oncological feasibility of envelope-preserving mastectomy after NACT, but they do not prove long-term equivalence. The increased risk of skin necrosis and longer hospitalization should be discussed during shared decision-making. Multicenter studies with longer follow-up, separate SSM and NSM analyses, reconstruction-matched comparison groups, and patient-reported outcomes are needed.

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