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Nipple-Sparing Mastectomy is Not Associated with a Delay of Adjuvant Treatment

Emily L. Albright, MD, Mary C. Schroeder, PhD, Kendra Foster, MS, Sonia L. Sugg, MD, Lillian M. Erdahl, MD, Ronald J. Weigel, MD, PhD, and Ingrid M. Lizarraga, MBBS
University of Iowa, Iowa, IA

Abstract

Background.—High-volume single-institution studies support the oncologic safety of nipple sparing mastectomy (NSM). Concerns remain regarding the increased potential for complications, recurrence, and delays to subsequent adjuvant therapy. A national database was used to examine treatment and outcomes for NSM patients.

Methods.—Women undergoing unilateral NSM or skin sparing mastectomy (SSM) for stage 0–4 breast cancer from 2004 to 2013 were identified from the National Cancer Database. Demographic and oncologic characteristics, short-term outcomes and time to local and systemic treatment were compared.

Results.—NSM was performed on 8173 patients: 8.7% were node positive, and for stage 1–4 disease, 10.6% were triple negative (TN) and 15.3% were HER2-positive. NSM patients were less likely than SSM patients to receive chemotherapy [CT] (37.4 vs. 43.4%) or radiation [PMRT] (15.6 vs. 16.9%), and were also more likely to present with clinically early-stage disease. NSM patients with high-risk features were more likely to receive CT in the neoadjuvant [NCT] than adjuvant setting [AC] (OR 3.76, 1.81, and 1.99 for clinical N2/3, TN, and HER2-positive disease, all $p < 0.001$). On multivariate analysis, NSM patients had a higher rate of pathologic complete response [pCR] (OR 1.41, $p < 0.001$). Readmission rate, positive margin rate and time to CT, PMRT or hormonal therapy were not increased for NSM compared to SSM patients.

Conclusions.—Over one third of NSM patients received chemotherapy and/or radiation. NSM patients with high-risk features were more likely to receive NAC and obtain a pCR. NSM patients did not experience worse outcomes or delayed adjuvant therapy compared to SSM.

Nipple sparing mastectomy (NSM) for the treatment of breast cancer is increasing in the United States. A recent analysis of the National Cancer Database (NCDB) found that 8.0% of all mastectomies with reconstruction done for cancer in 2013 were NSM.¹ Almost half of the NSM patients treated from 2010 to 2013 had high-risk features (tumors greater than 2 cm, node positive, HER2-positive, or high grade), which National Comprehensive Cancer Network (NCCN) guidelines caution should be contraindications for this procedure.^{1,2} Previous single institution studies and two meta-analyses have found no increase in loco-regional recurrence rates with NSM.^{3–7} However, the majority of NSM patients in those studies had lower risk disease. The patients with the longest follow up in those studies also

had stricter eligibility criteria with respect to tumor size, absence of nodal involvement and distance from the nipple.^{3,4} Concerns related to oncologic safety are based not only on the possibility of nipple areolar complex recurrence, but also on the relative technical difficulty of NSM, with greater potential for complications and delay to subsequent adjuvant therapy. Delay to adjuvant treatment is known to be associated with lower breast cancer specific survival.^{8–11} Regarding complications following NSM, a meta-analysis of 23 studies cited an overall 8.8% rate of nipple-areolar necrosis (range 0–41%), a 2.0% rate of nipple areolar loss, a 9.5% rate of skin flap necrosis and a 3.4% rate of expander-implant loss.⁴ However, these are outcomes reported by high volume centers. The national rates of these complications are likely much higher, as the NCDB report found that over three-quarters of the centers performing therapeutic NSM had done fewer than 10 cases over a four year period.¹

Based on these observations, we sought to investigate the impact of NSM on short-term outcomes using a large, multi-institutional dataset. We compared the positive margin rates, readmission rates, and time to therapy (surgery, adjuvant chemotherapy, radiation therapy, and adjuvant hormonal therapy) for patients who underwent NSM versus skin sparing mastectomy with immediate reconstruction (SSM). We performed subgroup analyses on those patients deemed high risk by clinical and pathologic factors.

METHODS

Data Source

The NCDB, established in 1989, is a nation-wide, facility-based, comprehensive clinical surveillance resource oncology data set jointly sponsored by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society that collects information annually on approximately 70% of all newly diagnosed cancers in the United States from more than 1500 CoC accredited facilities. Data collected includes patient characteristics, tumor characteristics, treatment and outcomes. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its CoC accredited facilities. Institutional review board approval was obtained.

Patient Selection

De-identified data from the NCDB was obtained for patients diagnosed with breast cancer between 2004 and 2013. We selected breast cancer patients who underwent mastectomy with reconstruction based on site-specific surgery codes as described in the Facility Oncology Database Standards (FORDS manual).¹² Patients with surgery code 30 (“removal of breast tissue without the nipple and areolar complex (NAC) or overlying skin. Patient may be considered to have undergone breast reconstruction”) were classified as having NSM. Patients were classified as having a SSM based on site-specific surgery codes 43–46, 53–56 and 64–67, which includes simple, modified radical and radical mastectomy, all with reconstruction and without removal of contralateral breast. These codes all involve removal of the NAC. Patients undergoing bilateral mastectomy were excluded because the coding in this procedure does not allow determination of whether a NSM was performed. Male patients, individuals without reconstruction and cT0 patients were excluded.

Data Analysis

Demographic, clinical, and treatment characteristics were identified for our study sample. Clinical and demographic data including age, Charlson comorbidity index, estrogen receptor (ER) status, HER2/neu receptor status and clinical (c) and pathological (p) tumor (T), nodal (N) and metastatic (M) stages were recorded. Treatment and outcome information including length of hospital stay (LOS), 30-day readmission rates, and receipt of chemotherapy, hormonal therapy, and post-mastectomy radiation therapy were recorded. Surgical margin status following mastectomy was also examined. In the NCDB, this is reported as positive or negative; however the location of the positive margin (eg skin, nipple or deep) is not specified. Time to therapy was also estimated from date of diagnosis and date of surgery using Kaplan-Meier estimators for various treatment combinations. In NCDB, only the first date of each treatment modality received is recorded. Pathologic complete response (pCR) rate was determined for a subsample of patients with invasive breast cancer and no evidence of distant metastases (cM0/0i+) who received neoadjuvant chemotherapy (NCT), and had known clinical and pathological staging information (cT, cN, pT, and pN, excluding cTisN0). pCR was defined as pathologic stage ypT0/ispN0pM0.

The proportion receiving NSM (of the sample with NSM or SSM) was calculated for each year and changes assessed and fit using Joinpoint Regression Program (version 4.2, Information Management Services, Incorporated; Calverton, MD) with log-linear models. Annual percent changes (APC) were estimated for the final selected model. Statistical analyses were performed with STATA MP, version 12.0 (StataCorp LP, College Station, TX). Demographic and clinical characteristics were compared by type of surgery using Chi-squared analyses. Kaplan-Meier curves of time to therapy were compared across type of mastectomy with a Log-rank test.

RESULTS

We identified 129,951 patients for analysis, with 8173 (6.3%) in the NSM group and 121,778 in the SSM group. NSM was performed from 2004 to 2007 at a steady rate of 2.2% (Fig. 1), increasing sharply after 2007 at an APC of 47.5 ($p < 0.001$).

Patient/tumor characteristics

Patient demographic and clinical characteristics/treatments are shown in Table 1. Median age for the two groups differed slightly (51 years old for NSM vs. 52 years old for the SSM patients, $p < 0.001$), but the NSM group were more likely to be < 45 years old at diagnosis (26% vs. 20.5%, $p < 0.001$). Most patients in both groups presented with invasive breast cancer (clinical stage 0 reported in 26% (2,125) of NSM and 20% (24,560) of all SSM patients). NSM was more likely to be performed in clinically early stage patients than SSM; those who presented with cTis or cT1 disease were 1.34 times more likely to receive NSM than SSM ($p < 0.001$) and those with cN0 disease were 1.55 times more likely ($p < 0.001$). In patients with invasive cancer (i.e. AJCC pathologic Stage I-IV), there was no significant difference in the rate of triple negative breast cancer (10.16 vs. 10.3%) or HER2-positive disease (15.3 vs. 16.2%) for NSM vs. SSM (Table 2).

Treatment Characteristics

Overall, NSM patients were less likely to receive adjuvant therapy. For those with known treatment information, surgery with no additional therapy was performed in 31.1% of NSM vs. 28.5% of SSM patients ($p < 0.001$). Chemotherapy and post-mastectomy radiation (PMRT) were also less common in the NSM vs. SSM group (38.4 vs. 45.1% and 15.6 vs. 16.9%, respectively, both $p < 0.001$) (Table 1). Patients with NSM were more likely to have PMRT alone without any other adjuvant treatment (1.3 vs. 0.5%, $p < 0.001$) as well as radiation and hormonal therapy (HT) without chemotherapy (2.9 vs. 1.5%, $p < 0.001$).

Despite receiving chemotherapy less often, patients selected for NSM were significantly more likely to have received their chemotherapy in a neoadjuvant setting than SSM patients (35.9 vs. 22.7%, $p < 0.001$). This is especially true for patients with clinically high-risk disease (cT3/4 tumors, cN2/3, triple negative or HER2-positive), with odds ratios (OR) of receiving NCT (vs AC) compared to SSM patients ranging from 1.75 for patients with cT3/T4 tumors to 3.76 for those with advanced nodal disease (cN2/3) (Table 3). For patients who received NCT, the pCR rate was markedly higher in the NSM group (25.8 vs. 14.5%, $p < 0.001$). This difference persisted after controlling for ER status, HER2/neu status, age, T stage and N stage (OR 1.41 for pCR in NSM compared to SSM, $p = 0.001$). The rate of PMRT after NAC did not differ significantly between groups (4.5 vs. 4.6%, $p = 0.523$).

Short Term Outcomes and Time to Treatment

NSM patients were less likely to have LOS ≥ 3 days (17.6 vs. 23.7%, $p < 0.001$) and less likely to have an unplanned readmission within 30 days (2.2 vs. 2.7%, $p < 0.001$). However, they also had a lower comorbidity burden as measured by the Charlson co-morbidity index ($p < 0.001$). On multivariate analysis including age, comorbidity index, stage, receptor status and receipt of NCT, both LOS and unplanned 30 day readmission remained lower for NSM. Of those with known surgical margin status, the rate of positive margins was similar for NSM (4.1%) and SSM (3.9%) patients ($p = 0.600$) and in those with positive margins there was no difference in microscopic versus macroscopic residual tumor.

There was no difference in time from surgery to adjuvant chemotherapy (AC) (Fig. 2a). Time to PMRT in patients who also received chemotherapy was separately evaluated, based on whether NCT or AC was administered. For both groups, there was no difference in time to PMRT either from date of diagnosis or date of surgery between SSM and NSM patients (Fig. 2b, c). Median time to HT was longer for SSM patients overall (a difference of 17 days between median days to therapy from date of diagnosis), driven by patients who received chemotherapy (Fig. 2d). Even so, the overall time to HT from diagnosis for all groups was within the 365 days endorsed by the National Quality Forum.¹³ Multivariate analyses of time to CT, PMRT or HT controlling for age, stage, comorbidity, receptor status and NCT confirmed no difference between NSM and SSM patients (results not shown).

DISCUSSION

This is the first study to report treatment patterns and short-term outcomes by mastectomy type for unilateral breast cancer patients undergoing reconstruction in a large multi-

institutional database. The NCDB captures 70% of new cancer diagnoses nationally in a wide range of treatment settings with a diverse geographic distribution, which helps illuminate real-world treatment trends in the United States. A recent analysis of NCDB data from 2010 to 2013 raised concerns that while NSM patients in general have less advanced disease than other patients with immediate reconstruction, a significant proportion had unfavorable clinicopathologic features as defined by the NCCN.¹ In our study of patients receiving therapeutic NSM from 2004 to 2013, the majority had invasive cancer, and 15.3% of those were HER2-positive, 10.1% were triple negative and 10.0% were node positive.

Current NCCN guidelines state that nipple-areolar sparing procedures are an option for carefully selected patients based on retrospective data for early-stage, biologically favorable breast cancer.² However, indications for NSM vary widely in the literature, and large case series increasingly describe the use of NSM for locally advanced disease.^{14–17} Only 3.5% of patients in our NSM population had T3/T4 tumors and 1.1% had N2/N3 disease. However, more than one-quarter of patients selected for NSM were ER negative or HER2-positive, and over one-third received chemotherapy, suggesting that a substantial proportion of NSM patients represent a higher risk cohort than would be recommended by guidelines.

There are multiple studies reporting worse overall and breast-cancer-specific survival in patients who experience a delay to chemotherapy after surgery.^{8,9} This is particularly the case for high-risk patients (triple negative, HER2-positive or stage 2/3 disease).⁶ While the NCDB does not collect data on surgical complications directly, we examined short term outcomes such as LOS, unplanned readmissions and time to adjuvant treatment after surgery, all of which may be influenced by surgical complexity and complication rate. LOS and readmission rates were slightly lower for NSM in both adjusted and unadjusted models, although we were unable to account for type of reconstruction, which is not consistently reported in the NCDB. NSM was not associated with a delay in delivery of adjuvant chemotherapy or hormonal therapy compared to SSM.

Within the group of patients who receive chemotherapy, those who require NCT typically have more advanced clinical disease or an unfavorable disease subtype compared to those who receive it in the adjuvant setting.² The use of NSM for patients receiving NCT is increasingly described in the literature.^{5–7,15} A recent series reported an increase in the proportion of therapeutic NSM patients receiving NCT from 8 to 21% over a 5-year period.¹⁶ In our study, 12.7% of NSM patients received NCT. Compared to SSM patients, patients selected for NSM were more likely to have received their chemotherapy prior to surgery. Our results suggest that, although a significant number of patients undergoing NSM are high risk at presentation, many of these were selected for NSM after receiving NCT. The higher proportion of pCR in the NSM group also suggests that within this high-risk group, NSM was reserved for patients with evidence of a good clinical response to NCT, which comprise a group that has historically been shown to have more favorable long-term outcomes.¹⁷

Patients at greatest risk for subsequent recurrence based on extent of disease require timely delivery of both chemotherapy and PMRT.² The consequences of delay to PMRT is poorly studied, although studies of breast conserving therapy suggest that loco-regional recurrence rates are higher when radiation is delivered more than 8 weeks after surgery, even in patients

with early stage disease.^{10,11} Reassuringly, we found that the subset of NSM patients who received both chemotherapy and PMRT did not have a longer time to radiation than their peers who underwent SSM, regardless of whether the chemotherapy was delivered in the adjuvant or neoadjuvant setting. Our results also support evidence from single institution studies that breast reconstruction is not associated with higher complication rates or delay to adjuvant therapy in patients who receive chemotherapy.^{18–20}

Our study has several important limitations. Accuracy of coding in the NCDB cannot be verified, and important clinical data such as HER2/neu status, T stage and N stage was incomplete for some patients. Additionally, it is likely that the current coding fails to capture all the NSM cases in this dataset. The American College of Surgeons recommends that NSM be billed using the Current Procedural Terminology codes for simple mastectomy, and currently the only billing code specific to nipple sparing (subcutaneous) mastectomy does not accurately reflect the modern oncologic operation.^{21,22} This may influence the wording of operative reports and hinder the effort of tumor registry abstracters to accurately differentiate SSM and NSM, leading to underreporting of the true rate of NSM in NCDB. We also excluded patients undergoing bilateral mastectomy as these codes do not indicate mastectomy type.¹² These limitations highlight the importance of prospectively maintained databases such as the American Society of Breast Surgeons NSM registry, and argue for creation of specific registry and billing codes.

This study adds to existing data on the oncologic safety of NSM. It provides insight into recent, short-term outcomes of therapeutic NSM in clinically and geographically diverse treatment settings across the country. We found that the use of NSM to treat breast cancer was increasing, and that a significant proportion of NSM patients had less favorable biologic features. Even so, our analysis showed that NSM was not associated with any worse short-term outcomes or a delay in time to adjuvant therapy.

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Years	APC	95% CI of APC		p-value
2004-2008	-0.08	-14.92	17.34	0.990
2008-2013	47.47	40.70	54.57	<0.001

FIG. 1.

Proportion of patients receiving nipple sparing mastectomy (NSM) by year of diagnosis and annual percent change (APC) in incidence

FIG. 2.

Time to treatment in days by type of mastectomy for the following treatments: **a** adjuvant chemotherapy (AC) from surgery date, **b** post-mastectomy radiation therapy (PMRT) following AC from diagnosis and surgery date, **c** PMRT following neoadjuvant chemotherapy (NCT) from diagnosis and surgery date, and **d** hormone therapy (HT) with and without chemotherapy from diagnosis date

TABLE 1

Patient demographic and clinical characteristics by type of mastectomy

	NSM (8173)		SSM (121,778)		<i>p</i> value
	<i>N</i>	%	<i>N</i>	%	
Age at time of diagnosis					
< 45	2122	26.0	24,968	20.5	< 0.001
45–54	2999	36.7	44,248	36.3	
55–65	1961	24.0	33,859	27.8	
65–69	577	7.1	10,658	8.8	
70+	514	6.3	8045	6.6	
Charlson Comorbidity Index					
0	7467	91.4	108,112	88.8	< 0.001
1	632	7.7	12,076	9.9	
2	74	0.9	1590	1.3	
ER status					
Negative	1276	15.6	21,459	17.6	< 0.001
Positive	6271	76.7	89,803	73.7	
Unknown	626	7.7	10,516	8.6	
HER2/neu status ^a					
Negative	3381	41.4	34,072	28.0	< 0.001
Positive	609	7.5	6599	5.4	
Unknown	4183	51.2	81,107	66.6	
Clinical T stage					
Tis	1998	24.4	24,221	19.9	< 0.001
T1	3076	37.6	38,020	31.2	
T2	1442	17.6	21,610	17.7	
T3	242	3.0	4940	4.1	
T4	41	0.5	1903	1.6	
Unknown	1374	16.8	31,084	25.5	
Clinical N stage					
N0	6419	78.5	79,513	65.3	< 0.001

	NSM (8173)		SSM (121,778)		<i>p</i> value	
	<i>N</i>	%	<i>N</i>	%		
N1	622	7.6	10,854	8.9		
N2	58	0.7	1932	1.6		
N3	36	0.4	937	0.8		
Unknown	1038	12.7	28,542	23.4		
Clinical M stage						
M0	7584	92.8	117,008	96.1	< 0.001	
M1	31	0.4	988	0.8		
Unknown	558	6.8	3782	3.1		
Pathologic complete response ^b						
Yes	205	25.8	1082	14.5	< 0.001	
No	589	74.2	6379	85.5		
Surgical margins						
Negative	7524	92.1	115,683	95.0	< 0.001	
Positive	318	3.9	4740	3.9		
Unknown	331	4.0	1355	1.1		
Extent of positive margins ^c						
Microscopic residual tumor	205	64.5	2868	60.5	0.216	
Macroscopic residual tumor	9	2.8	103	2.2		
Residual tumor, NOS	104	32.7	1769	37.3		
Length of hospital stay (days)						
0	1698	23.1	17,494	15.7	< 0.001	
1	2512	34.1	37,869	34.0		
2	1853	25.2	28,949	26.0		
3	592	8.0	11,917	10.7		
4 or more	703	9.6	15,295	13.7		
30-day readmission, unplanned						
No	7882	96.4	115,402	94.8	< 0.001	
Yes	177	2.2	3305	2.7		
Unknown	114	1.4	3071	2.5		
Chemotherapy (CT)						

	NSM (8173)		SSM (121,778)		p value
	N	%	N	%	
No	4914	60.1	64,454	52.9	<0.001
Yes	3065	37.5	52,912	43.4	
Unknown	194	2.4	4412	3.6	
Timing of CT					
Neoadjuvant	1041	34.0	11,114	21.0	<0.001
Adjuvant	1863	60.8	37,877	71.6	
Unknown	161	5.3	3921	7.4	
Hormonal therapy (HT)					
No	3569	43.7	51,025	41.9	0.002
Yes	4163	50.9	63,434	52.1	
Unknown	441	5.4	7319	6.0	
Timing of HT					
Neoadjuvant	243	5.8	2592	4.1	<0.001
Adjuvant	3671	88.2	55,383	87.3	
Unknown	249	6.0	5459	8.6	
Post-mastectomy radiation therapy (PMRT)					
No	6777	82.9	97,537	80.1	<0.001
Yes	1276	15.6	20,531	16.9	
Unknown	120	1.5	3710	3.0	
Timing of CT, for those with PMRT					
Neoadjuvant	367	29.7	5655	28.7	<0.001
Adjuvant	521	42.2	11,693	59.4	
Unknown	14	1.1	110	0.6	
No CT	333	27.0	2221	11.3	

^aSample includes those with invasive disease (AJCC pathologic stage I–IV)

^bSample includes known cT, cN, pT, pN, excluding cTisN0 and pM1, who received neoadjuvant chemotherapy

^cSample only includes those with positive margins

TABLE 2

Type of mastectomy for high-risk patient groups

	NSM	SSM	Total	<i>p</i> value ^a
cT3–4	283 (4.2%)	6843 (7.5%)	97,493	<0.001
cN2–3	94 (1.3%)	2869 (3.1%)	100,371	<0.001
cN+	716 (10.0%)	13,723 (14.7%)	100,371	<0.001
Her2-positive ^b	609 (15.3%)	6599 (16.2%)	44,661	0.115
Triple negative breast cancer	424 (10.6%)	4104 (10.1%)	44,566	0.301

For each high-risk patient group, sample includes those with known information. The percent of patients with a particular high-risk characteristic is reported in parentheses. "Total" refers to all patients in the sample with known information for that characteristic

^aFrom chi-squared test comparing NSM with SSM

^bHER2/neu status identified for those with invasive (AJCC pathologic Stage I-IV) disease only

TABLE 3

Odds ratio (OR) of NSM patients receiving neoadjuvant chemotherapy (vs. adjuvant chemotherapy) compared to SSM patients, by high-risk patient group

High risk group	OR	95% CI	<i>p</i> value
cT34	1.75	1.27–2.42	<0.001
cN23	3.76	2.14–6.60	<0.001
clinical node positive	2.12	1.78–2.52	<0.001
HER2-positive ^a	1.81	1.47–2.23	<0.001
Triple negative breast cancer ^a	1.99	1.59–2.49	<0.001

^a Her2/neu status identified for those with invasive (AJCC pathologic Stage I–IV) disease only