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Outcomes of > 1300 Nipple-Sparing Mastectomies with Immediate Reconstruction: The Impact of Expanding Indications on Complications

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ABSTRACT

Background. The enhanced esthetics and demonstrated oncologic safety of nipple-sparing mastectomy (NSM) in selected patients have resulted in increased rates among patients with locally advanced breast cancer and/or additional risk factors (obesity, prior radiation, surgery). Limited data exist on complication and reconstruction success rates in a contemporary patient cohort with expanded indications for NSM.

Methods. With institutional review board (IRB) approval, patients treated from 2009 to 2017 with NSM were identified from our prospective breast surgery registry. Main outcomes were 30-day complications requiring treatment and 1-year reconstruction failure rates. Risk factors were assessed using logistic regression.

Results. We evaluated 1301 breasts in 769 women undergoing NSM for cancer ($n = 555$) or risk reduction ($n = 746$) with median age of 48 (range 21–77) years. The overall 30-day complication rate was 7.5% (97/1301 breasts) and declined from 14.8% in 2009 to 6.3% in 2017 ($p < 0.001$), while the proportion of patients with obesity ($p = 0.007$) and treated with neoadjuvant chemotherapy ($p < 0.001$) increased. Prior radiation [odds ratio (OR) 2.35, $p = 0.04$], recent/current smoking (OR 3.37, $p < 0.001$), and body mass index (BMI) (OR 1.28 per 5-kg/m^2 increase, $p = 0.03$) significantly increased 30-day complication rates. Reconstruction success at 1 year was 96.7%. Prior radiation (OR 5.65, $p < 0.001$), axillary surgery (OR 2.55, $p = 0.006$), and postoperative adjuvant radiation (OR 3.22, $p = 0.007$) significantly affected 1-year reconstruction failure.

Conclusion. The 30-day complication rates of NSM decreased, despite broadened indications among higher-risk patients over time. These data confirm a team learning curve with NSM and also demonstrate that the nipple-sparing approach is suitable for appropriately selected higher-risk patients for both risk reduction and cancer treatment.

The uptake of nipple-sparing mastectomy (NSM) for both breast cancer treatment and risk reduction over the past decade has been remarkably rapid.[1–3] While subcutaneous mastectomy with nipple preservation was described more than 50 years ago for women with benign disease, that approach deliberately retains varying amounts of breast tissue under the nipple–areolar complex and has been shown to be inadequate for cancer treatment.[4,5] Contemporary NSM involves preservation of the nipple–areolar complex and skin envelope with its blood supply while resecting all gross visible breast tissue. The enhanced esthetics of this approach, supported by advances in reconstructive techniques, have spurred demand for the procedure. Initial guidelines suggested this approach be limited to women with favorable patient characteristics and, when used to treat cancer rather than for risk reduction, limited to cancer patients with favorable tumor

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characteristics.[2,6–8] Such criteria included non-high-grade, small, and peripheral tumors at least 2 cm from the nipple on imaging.[9–14]

More recently, with recognition of the influence of efficacious systemic therapies in diminishing local as well as distant recurrence rates, these criteria have been challenged.[2,6,15–18] Further, as experienced teams have gained technical expertise with NSM, patient factors initially felt to contraindicate NSM such as prior breast operations and radiation, larger breast size, ptosis, and obesity have been reconsidered.[6,18–21] Current National Comprehensive Cancer Network (NCCN) guidelines simply state that "experienced multidisciplinary teams may consider nipple–areolar complex-sparing procedures for carefully selected patients with breast cancer" with mandatory pathologic assessment of the nipple margin, while noting that retrospective reviews assessing outcomes have utilized the more restrictive criteria for offering NSM.[22]

Thus, indications for NSM have broadened over time. Yet, NSM is a technically challenging operation. While several earlier publications have suggested an individual and/or team learning curve associated with NSM,[1,2,15,23] little is known about the effect of broadened indications, in terms of both patient and tumor factors, on complication rates once this initial experience is obtained. Thus, it remains largely unknown how increasing inclusion of higher-risk patients with more advanced disease impacts complication rates and, ultimately, the success of reconstruction. Therefore, the aim of this study is to evaluate complication and reconstructive failure rates over time as indications for NSM and patient selection criteria have evolved.

METHODS

With IRB approval, we identified patients treated with NSM from 2009 to 2017 from our prospective breast surgery registry. Our main outcome measure was the rate of 30-day complications requiring treatment or delaying immediate reconstruction. We defined these as surgical-site infection requiring antibiotics or drainage, hematoma or seroma requiring operation, and necrosis requiring debridement or hyperbaric therapy or resulting in nipple loss. Separately, we assessed the proportion of patients with unplanned reoperation for any reason at any time after their index operation (complication or positive margin, whether within 30 days or thereafter). We also assessed the success of reconstruction at 1 year. Patients with a tissue expander or permanent prosthesis in place, or those who had successfully undergone autologous reconstruction 1 year following their index operation, were considered reconstructive successes. Patients who had loss of tissue expander, permanent prosthesis, or flap and remained unreconstructed either by choice or who had not yet undergone an autologous reconstruction at 1 year from the index operation were considered reconstructive failures.

Selection criteria for consideration of NSM in our practice were as previously published.[2,6] Variables evaluated included patient (age, presence of diabetes, BMI, smoking history, prior breast surgery, prior radiation, and operative indication), tumor (T and N stage), and treatment (incision type, reconstruction, axillary surgery, use of neoadjuvant chemotherapy, and postmastectomy radiation) factors. Patients were classified as node positive if they were either biopsy-confirmed clinically node positive (cN+) or pathologically node positive; neoadjuvant patients who were cN+ with pathologic complete response to treatment (*y*pN0) were counted as having node-positive disease. Stage was classified according to American Joint Committee on Cancer (AJCC) 7th edition.

Statistical Analysis

Trends over time were assessed using Cochran–Armitage tests for linear trend for binary variables and Spearman rank correlations for continuous or ordinal variables. Chi-square tests and Wilcoxon rank-sum tests were used for other tests of association with calendar year. Risk factors were assessed using logistic regression for the outcomes of 30-day complications requiring treatment and reconstruction failure within 1 year. Multivariable analysis was conducted using the best subset selection approach based on the score criterion. Analysis was performed using SAS (version 9.4). p values < 0.05 were considered statistically significant.

RESULTS

Patient Population

Among 1353 breasts planned for NSM, 1301 breasts (769 patients) underwent NSM, while 52 cases were converted intraoperatively to skin-sparing (SSM) or areolar-sparing mastectomy (ASM) due to intraoperative frozen-section pathology showing neoplasm (35) or atypia (7), or concerns regarding nipple perfusion (5) or symmetry (5). The preoperative indication for NSM was cancer treatment in 542 and risk reduction in 759 breasts, but occult malignancies were identified at surgery in 13/759 (1.7%) NSMs performed for risk reduction. Thus, the final diagnosis was cancer in 555 breasts and risk reduction in 746 breasts.

Median patient age was 48 (range 21–77) years. Of 769 NSM patients, 524 (68.1%) underwent synchronous

TABLE 1 Baseline characteristics of 769 patients undergoing NSM

	2009 (*N* = 35)	2010 (*N* = 53)	2011 (*N* = 61)	2012 (*N* = 52)	2013 (*N* = 84)	2014 (*N* = 107)	2015 (*N* = 148)	2016 (*N* = 130)	2017 (*N* = 99)	Total (*N* = 769)	*p* value*
Age, years											0.60
Median	47	48	48	47	47	46	49	47.5	48	48	
Range	(21–66)	(24–67)	(24–65)	(26–74)	(21–75)	(22–75)	(21–74)	(27–77)	(25–76)	(21–77)	
Age category											0.23
< 50 years	23 (65.7%)	29 (54.7%)	34 (55.7%)	35 (67.3%)	51 (60.7%)	62 (57.9%)	77 (52.0%)	73 (56.2%)	55 (55.6%)	439 (57.1%)	
50–64 years	11 (31.4%)	22 (41.5%)	26 (42.6%)	13 (25.0%)	29 (34.5%)	39 (36.4%)	63 (42.6%)	53 (40.8%)	37 (37.4%)	293 (38.1%)	
≥ 65 years	1 (2.9%)	2 (3.8%)	1 (1.6%)	4 (7.7%)	4 (4.8%)	6 (5.6%)	8 (5.4%)	4 (3.1%)	7 (7.1%)	37 (4.8%)	
BMI, kg/m^2 (*n* = 3 missing)											< 0.001
Median	24.8	22.2	22	23.7	23.9	26	25	24	25	24.1	
Range	(19.0–34.7)	(17.9–32.6)	(17.8–36.3)	(19.3–42.2)	(17.6–37.7)	(19.0–43.0)	(17.0–39.0)	(14.0–41.0)	(18.0–52.0)	(14.0–52.0)	
BMI category, kg/m^2 (*n* = 3 missing)											< 0.001
< 25	19 (54.3%)	37 (69.8%)	50 (82.0%)	36 (70.6%)	53 (64.6%)	42 (39.3%)	71 (48.0%)	68 (52.3%)	43 (43.4%)	419 (54.7%)	
25–29	10 (28.6%)	10 (18.9%)	5 (8.2%)	11 (21.6%)	21 (25.6%)	46 (43.0%)	55 (37.2%)	36 (27.7%)	33 (33.3%)	227 (29.6%)	
30–34	6 (17.1%)	6 (11.3%)	4 (6.6%)	3 (5.9%)	6 (7.3%)	12 (11.2%)	17 (11.5%)	17 (13.1%)	18 (18.2%)	89 (11.6%)	
≥ 35	0 (0.0%)	0 (0.0%)	2 (3.3%)	1 (2.0%)	2 (2.4%)	7 (6.5%)	5 (3.4%)	9 (6.9%)	5 (5.1%)	31 (4.0%)	
BMI ≥ 30 kg/m^2											
No	29 (82.9%)	47 (88.7%)	55 (90.2%)	47 (92.2%)	74 (90.2%)	88 (82.2%)	126 (85.1%)	104 (80.0%)	76 (76.8%)	646 (84.3%)	0.007
Yes	6 (17.1%)	6 (11.3%)	6 (9.8%)	4 (7.8%)	8 (9.8%)	19 (17.8%)	22 (14.9%)	26 (20.0%)	23 (23.2%)	120 (15.7%)	
Smoking status (*n* = 2 missing)											0.40
Never	28 (80.0%)	36 (69.2%)	43 (70.5%)	41 (78.8%)	61 (73.5%)	75 (70.1%)	111 (75.0%)	95 (73.1%)	65 (65.7%)	555 (72.4%)	
Past (quit > 1 year prior)	5 (14.3%)	8 (15.4%)	12 (19.7%)	8 (15.4%)	18 (21.7%)	22 (20.6%)	27 (18.2%)	24 (18.5%)	23 (23.2%)	147 (19.2%)	
Recent (within 1 year prior)	2 (5.7%)	6 (11.5%)	5 (8.2%)	2 (3.8%)	3 (3.6%)	9 (8.4%)	10 (6.8%)	11 (8.5%)	11 (11.1%)	59 (7.7%)	
Current	0 (0.0%)	2 (3.8%)	1 (1.6%)	1 (1.9%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.8%)	
Recent or current smoker (*n* = 2 missing)											0.96
No	33 (94.3%)	44 (84.6%)	55 (90.2%)	49 (94.2%)	79 (95.2%)	97 (90.7%)	138 (93.2%)	119 (91.5%)	88 (88.9%)	702 (91.5%)	
Yes	2 (5.7%)	8 (15.4%)	6 (9.8%)	3 (5.8%)	4 (4.8%)	10 (9.3%)	10 (6.8%)	11 (8.5%)	11 (11.1%)	65 (8.5%)	
Diabetes mellitus											0.27
No	35 (100.0%)	53 (100.0%)	60 (98.4%)	51 (98.1%)	81 (96.4%)	105 (98.1%)	144 (97.3%)	128 (98.5%)	96 (97.0%)	753 (97.9%)	
Yes	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.9%)	3 (3.6%)	2 (1.9%)	4 (2.7%)	2 (1.5%)	3 (3.0%)	16 (2.1%)	
Preoperative cancer diagnosis in either breast											0.08
No	9 (25.7%)	13 (24.5%)	16 (26.2%)	22 (42.3%)	18 (21.4%)	28 (26.2%)	32 (21.6%)	24 (18.5%)	22 (22.2%)	184 (23.9%)	
Yes	26 (74.3%)	40 (75.5%)	45 (73.8%)	30 (57.7%)	66 (78.6%)	79 (73.8%)	116 (78.4%)	106 (81.5%)	77 (77.8%)	585 (76.1%)	
Treated with neoadjuvant chemotherapy											< 0.001
No	35 (100.0%)	49 (92.5%)	56 (91.8%)	50 (96.2%)	71 (84.5%)	88 (82.2%)	125 (84.5%)	92 (70.8%)	73 (73.7%)	639 (83.1%)	
Yes	0 (0.0%)	4 (7.5%)	5 (8.2%)	2 (3.8%)	13 (15.5%)	19 (17.8%)	23 (15.5%)	38 (29.2%)	26 (26.3%)	130 (16.9%)	

*p value for linear association between each factor and calendar year

bilateral NSM, performed for bilateral cancer in 25, unilateral cancer with contralateral risk-reducing mastectomy in 330, and bilateral risk reduction in 169 (Table 1). The latter were performed for high-risk genetic mutation in 68 cases, including deleterious mutations in *BRCA1* (39), *BRCA2* (27), *PALB2* (1), and *CDH1* (1). Median BMI was 24 (range 14–52) kg/m^2; 15.7% had BMI $\geq$ 30 kg/m^2. Recent or current smokers accounted for 8.5% of the study population, and 2.1% of patients were diabetic. Among these patient factors, only BMI changed significantly over the study period, with the proportion of patients with BMI $\geq$ 30 kg/m^2 increasing from 17.1 to 23.2% from 2009 to 2017 ($p = 0.007$) (Fig. 1). Of all patients, 16.9% were treated with neoadjuvant chemotherapy prior to NSM (22.3% of patients with preoperative diagnosis of cancer), which increased significantly over the study period from 0% to 26.3% of all patients (0% of those with a preoperative cancer diagnosis in 2009 versus 33.8% in 2017) ($p < 0.001$) (Fig. 1).

Clinical Features

Clinical features of the patients undergoing NSM are summarized in Table 2. A total of 4.5% of breasts had history of prior chest wall/breast or mantle radiation, and 21.2% breasts had undergone a prior operation. Inclusion of patients who received prior radiation did vary over the study period ($p < 0.001$) but not in a strictly linearly increasing or decreasing manner; 0% of the breasts selected for NSM in 2009–2010 had prior radiation, then this number increased steadily from 1.9% in 2011 up to 9.0% in 2014, followed by a decrease to 4.4% in 2015, 3.6% in 2016, and 1.1% in 2017. Clinical tumor category overall was most commonly cT1 (42.8%), but increasing calendar year was associated ($p = 0.001$) with higher clinical stages (80% cTis/cT1 in 2009 versus 61% cTis/cT1 in 2017) (Table 2). Node-positive disease was present in 27.4% of those with cancer as final diagnosis, and this percentage did not increase significantly over time ($p = 0.59$).

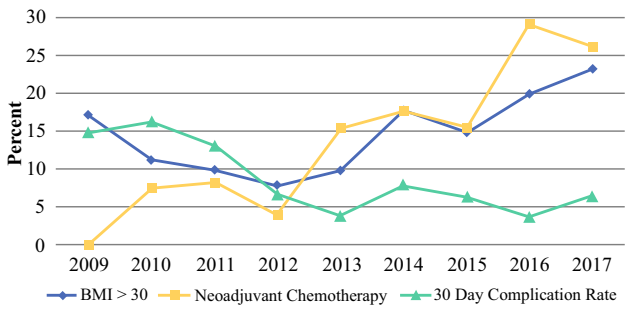

FIG. 1 Year-to-year change in patient BMI, administration of neoadjuvant chemotherapy, and 30-day complication rates in 1301 nipple-sparing mastectomies

Treatment

As shown in Table 2, the most commonly used incision was inframammary fold (53% overall, increasing from 13% of 2009 NSMs to 75.9% of 2017 NSMs) and incision type varied substantially over time ($p < 0.001$). Axillary surgery consisted of sentinel lymph node biopsy only in 422 (32.4%), sentinel lymph node biopsy and axillary dissection in 62 (4.8%), or axillary dissection in 39 (3.0%); the remaining 778 breasts (59.8%), mostly those undergoing risk-reducing NSM, did not have ipsilateral axillary surgery. Immediate reconstruction was performed in 1281/1301 (98.5%) of cases, delayed reconstruction in 15/1301 (1.2%), and no reconstruction in 5/1301 breasts (4 patients) per patient preference (Fig. 2). The most common type of reconstruction was placement of tissue expanders in 1152 (88.5%), followed by direct to implant in 99 (7.6%), autologous reconstruction in 30 (2.3%), Goldilocks inferior pedicle dermal flap in 13 (1.0%), and fat grafting only in 2 breasts (1 patient). Intraoperative indocyanine green angiography was performed in 52.0% overall, but this changed over time from 0% in 2009–2010, to 7.5% in 2011, then > 50% of NSM cases each year thereafter. Acellular dermal matrix was utilized in the majority (96.2%) of tissue expander-based reconstructions. The proportion of breasts treated with postmastectomy radiation (PMRT) was 8.3% overall (18.2% of breasts with cancer), and this percentage increased significantly over time from 3.7% in 2009 to 12.1% in 2017 ($p < 0.001$).

Outcomes

The overall rate of 30-day complications requiring treatment was 7.5% (97/1301 breasts). The most commonly observed complication was skin necrosis, occurring in 55 breasts (4.2%). Of the 55 breasts with mastectomy flap necrosis, 22 received hyperbaric oxygen therapy, 20 required debridement, 7 required delay of reconstruction, and 6 (0.5%) required nipple excision. Surgical-site infection or cellulitis requiring treatment occurred in 19 breasts (1.5%), hematoma in 13 (1.0%), and seroma requiring drainage in 10 (0.8%). Unplanned reoperation was required in 86 breasts (6.6%). The 30-day complication rate declined from 14.8% in 2009 to 6.3% in 2017 ($p < 0.001$) (Fig. 1). Among the 1296 reconstructed breasts, reconstruction success at 1 year was 96.7% (1253/1296) overall and increased significantly over the study period from 87.0% in 2009 to 100% in 2017 ($p < 0.001$).

TABLE 2 Clinical characteristics of 1301 breasts undergoing NSM

	2009 (*N* = 54)	2010 (*N* = 86)	2011 (*N* = 106)	2012 (*N* = 90)	2013 (*N* = 131)	2014 (*N* = 188)	2015 (*N* = 252)	2016 (*N* = 220)	2017 (*N* = 174)	Total (*N* = 1301)	*p* value*
Preoperative cancer diagnosis											0.04
No	29 (53.7%)	50 (58.1%)	67 (63.2%)	65 (72.2%)	77 (58.8%)	116 (61.7%)	148 (58.7%)	115 (52.3%)	92 (52.9%)	759 (58.3%)	
Yes	25 (46.3%)	36 (41.9%)	39 (36.8%)	25 (27.8%)	54 (41.2%)	72 (38.3%)	104 (41.3%)	105 (47.7%)	82 (47.1%)	542 (41.7%)	
Final pathologic diagnosis											0.09
Benign disease	28 (51.9%)	49 (57.0%)	66 (62.3%)	64 (71.1%)	74 (56.5%)	113 (60.1%)	147 (58.3%)	113 (51.4%)	92 (52.9%)	746 (57.3%)	
Malignant disease	26 (48.1%)	37 (43.0%)	40 (37.7%)	26 (28.9%)	57 (43.5%)	75 (39.9%)	105 (41.7%)	107 (48.6%)	82 (47.1%)	555 (42.7%)	
Prior breast or chest wall radiation (*n* = 3 missing)											0.87
No	54 (100.0%)	86 (100.0%)	101 (98.1%)	83 (92.2%)	120 (91.6%)	171 (91.0%)	241 (95.6%)	212 (96.4%)	172 (98.9%)	1240 (95.5%)	
Yes	0 (0.0%)	0 (0.0%)	2 (1.9%)	7 (7.8%)	11 (8.4%)	17 (9.0%)	11 (4.4%)	8 (3.6%)	2 (1.1%)	58 (4.5%)	
Prior ipsilateral breast operation											0.72
No	44 (81.5%)	70 (81.4%)	89 (84.0%)	74 (82.2%)	95 (72.5%)	136 (72.3%)	196 (77.8%)	184 (83.6%)	137 (78.7%)	1025 (78.8%)	
Yes	10 (18.5%)	16 (18.6%)	17 (16.0%)	16 (17.8%)	36 (27.5%)	52 (27.7%)	56 (22.2%)	36 (16.4%)	37 (21.3%)	276 (21.2%)	
Clinical T category (among breasts with preoperative cancer diagnosis, *n* = 7 missing)											0.001
cTis	10 (40.0%)	12 (33.3%)	12 (31.6%)	7 (29.2%)	14 (25.9%)	16 (22.5%)	29 (28.2%)	25 (24.0%)	14 (17.5%)	139 (26.0%)	
cT1	10 (40.0%)	18 (50.0%)	18 (47.4%)	12 (50.0%)	25 (46.3%)	29 (40.8%)	41 (39.8%)	41 (39.4%)	35 (43.8%)	229 (42.8%)	
cT2	4 (16.0%)	5 (13.9%)	7 (18.4%)	5 (20.8%)	13 (24.1%)	18 (25.4%)	30 (29.1%)	35 (33.7%)	26 (32.5%)	143 (26.7%)	
cT3	1 (4.0%)	1 (2.8%)	1 (2.6%)	0 (0.0%)	2 (3.7%)	8 (11.3%)	3 (2.9%)	3 (2.9%)	5 (6.3%)	24 (4.5%)	
Axillary operation											0.2
None	30 (55.6%)	57 (66.3%)	67 (63.2%)	65 (72.2%)	75 (57.3%)	119 (63.3%)	150 (59.5%)	121 (55.0%)	94 (54.0%)	778 (59.8%)	
SLN	16 (29.6%)	21 (24.4%)	33 (31.1%)	20 (22.2%)	48 (36.6%)	56 (29.8%)	86 (34.1%)	76 (34.5%)	66 (37.9%)	422 (32.4%)	
SLN & ALND	5 (9.3%)	4 (4.7%)	4 (3.8%)	3 (3.3%)	4 (3.1%)	6 (3.2%)	8 (3.2%)	19 (8.6%)	9 (5.2%)	62 (4.8%)	
ALND	3 (5.6%)	4 (4.7%)	2 (1.9%)	2 (2.2%)	4 (3.1%)	7 (3.7%)	8 (3.2%)	4 (1.8%)	5 (2.9%)	39 (3.0%)	
Node-positive disease (among breasts with malignant final diagnosis)											0.59
No	17 (65.4%)	25 (67.6%)	33 (82.5%)	18 (69.2%)	47 (82.5%)	54 (72.0%)	81 (77.1%)	69 (64.5%)	59 (72.0%)	403 (72.6%)	
Yes	9 (34.6%)	12 (32.4%)	7 (17.5%)	8 (30.8%)	10 (17.5%)	21 (28.0%)	24 (22.9%)	38 (35.5%)	23 (28.0%)	152 (27.4%)	
Incision											< 0.0001
Inframammary	7 (13.0%)	30 (34.9%)	46 (43.4%)	29 (32.2%)	56 (42.7%)	93 (49.5%)	139 (55.2%)	157 (71.4%)	132 (75.9%)	689 (53.0%)	
Radial	3 (5.6%)	8 (9.3%)	36 (34.0%)	29 (32.2%)	46 (35.1%)	59 (31.4%)	79 (31.3%)	42 (19.1%)	28 (16.1%)	330 (25.4%)	
Periareolar	44 (81.5%)	48 (55.8%)	24 (22.6%)	26 (28.9%)	24 (18.3%)	13 (6.9%)	12 (4.8%)	7 (3.2%)	7 (4.0%)	205 (15.8%)	
Reduction	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)	3 (2.3%)	19 (10.1%)	16 (6.3%)	9 (4.1%)	5 (2.9%)	54 (4.2%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.4%)	2 (1.5%)	4 (2.1%)	6 (2.4%)	5 (2.3%)	2 (1.1%)	23 (1.8%)	

TABLE 2 continued

	2009 (*N* = 54)	2010 (*N* = 86)	2011 (*N* = 106)	2012 (*N* = 90)	2013 (*N* = 131)	2014 (*N* = 188)	2015 (*N* = 252)	2016 (*N* = 220)	2017 (*N* = 174)	Total (*N* = 1301)	*p* value*
Acellular dermal matrix											0.97
No	2 (3.7%)	8 (9.3%)	9 (8.5%)	9 (10.0%)	5 (3.8%)	21 (11.2%)	15 (6.0%)	13 (5.9%)	16 (9.2%)	98 (7.5%)	
Yes	52 (96.3%)	78 (90.7%)	97 (91.5%)	81 (90.0%)	126 (96.2%)	167 (88.8%)	237 (94.0%)	207 (94.1%)	158 (90.8%)	1203 (92.5%)	
Intraoperative indocyanine green angiography											< 0.001
No	54 (100.0%)	86 (100.0%)	98 (92.5%)	28 (31.1%)	30 (22.9%)	73 (38.8%)	117 (46.4%)	87 (39.5%)	52 (29.9%)	625 (48.0%)	
Yes	0 (0.0%)	0 (0.0%)	8 (7.5%)	62 (68.9%)	101 (77.1%)	115 (61.2%)	135 (53.6%)	133 (60.5%)	122 (70.1%)	676 (52.0%)	
Type of reconstruction											< 0.0001
None	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.4%)	
Immediate implant	0 (0.0%)	8 (9.3%)	14 (13.2%)	22 (24.4%)	14 (10.7%)	6 (3.2%)	9 (3.6%)	20 (9.1%)	6 (3.4%)	99 (7.6%)	
Tissue expander	54 (100.0%)	78 (90.7%)	90 (84.9%)	61 (67.8%)	110 (84.0%)	166 (88.3%)	239 (94.8%)	192 (87.3%)	162 (93.1%)	1152 (88.5%)	
Autologous	0 (0.0%)	0 (0.0%)	1 (0.9%)	7 (7.8%)	5 (3.8%)	11 (5.9%)	4 (1.6%)	2 (0.9%)	0 (0.0%)	30 (2.3%)	
Goldilocks	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)	1 (0.5%)	0 (0.0%)	4 (1.8%)	6 (3.4%)	13 (1.0%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	0 (0.0%)	2 (0.2%)	
Postmastectomy radiation therapy											< 0.001
No	52 (96.3%)	81 (94.2%)	102 (96.2%)	88 (97.8%)	124 (94.7%)	170 (90.4%)	232 (92.1%)	191 (86.8%)	153 (87.9%)	1193 (91.7%)	
Yes	2 (3.7%)	5 (5.8%)	4 (3.8%)	2 (2.2%)	7 (5.3%)	18 (9.6%)	20 (7.9%)	29 (13.2%)	21 (12.1%)	108 (8.3%)	

*p value for linear association between each factor and calendar year in the case of continuous, ordinal, and binary variables. For multilevel, nonordinal, categorical variables, the p value is for a Chi-square test of any difference among calendar years

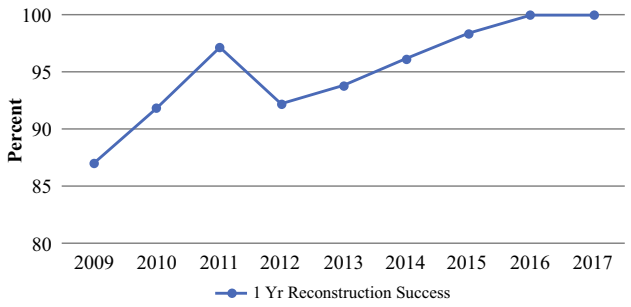

FIG. 2 Year-to-year change in successful reconstruction at 1 year in 1301 nipple-sparing mastectomies

Risk Factors

This decreasing 30-day complication requiring treatment rate was seen despite a significant increase over the study period in the proportion of patients with obesity and treatment with neoadjuvant chemotherapy. Univariate and multivariable associations for patient and clinical risk factors are presented in Table 3. On multivariable analysis, prior radiation (OR 2.35, $p = 0.04$), higher BMI (OR 1.28 per 5-kg/m^2 increase, $p = 0.03$), and recent/current smoking (OR 3.37, $p < 0.001$) significantly increased the risk of 30-day complications. Variables associated with reconstruction failure at 1 year among reconstructed breasts included axillary surgery (OR 2.55, $p = 0.006$), as well as both prior radiation (OR 5.65, $p < 0.001$) and adjuvant radiation therapy (OR 3.22, $p = 0.007$).

DISCUSSION

The results of this study show that NSM can be performed safely with acceptable 30-day complication rates in a large, modern cohort of higher-risk patients treated by a multidisciplinary group utilizing an integrated team of breast surgical oncologists experienced in performing NSM along with dedicated breast reconstructive plastic surgeons. We also show that reconstructive success is favorable following NSM even if expanded patient selection criteria are applied. Our impression is that these data highlight the team learning curve associated with NSM in terms of patient selection, surgical judgment, technical expertise, and perioperative management.

Our overall complication rates compare favorably with previous reports and were increased among patients with prior radiation and obesity and current/recent smokers. The overall postoperative complication rate for NSM from recent studies is approximately 20–30% and varies based on timing and definitions, with the rate of complications requiring treatment remaining at about 10–12%.[1,15,24–26] A recent metaanalysis and systematic review of NSM with

TABLE 3 Logistic regression analysis of the association of clinical risk factors with outcomes

	30-Day complication requiring treatment or delay of planned IBR				1-Year reconstruction failure			
	Univariate		Multivariable		Univariate		Multivariable	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Surgery year, per 1-year increase	0.84 (0.77–0.92)	< 0.001	0.82 (0.75–0.90)	< 0.001	0.69 (0.61–0.79)	< 0.001	0.64 (0.56–0.74)	< 0.001
Age, per 10-year increase	1.14 (0.93–1.40)	0.22			1.07 (0.79–1.45)	0.65		
BMI, per 5-kg/m^2 increase	1.19 (0.97–1.46)	0.09	1.28 (1.03–1.58)	0.03	0.92 (0.66–1.29)	0.63		
BMI ≥ 30 versus < 30 kg/m^2	1.40 (0.83–2.35)	0.21			0.47 (0.15–1.41)	0.18		
Recent (within 1 year) or current smoking, yes versus no	3.29 (1.93–5.61)	< 0.001	3.37 (1.95–5.81)	< 0.001	0.93 (0.30–2.83)	0.90		
Diabetes mellitus, yes versus no	0.67 (0.12–3.59)	0.64			0.49 (0.03–8.64)	0.63		
Prior radiation, yes versus no	2.17 (1.01–4.65)	0.048	2.35 (1.04–5.33)	0.04	4.21 (1.73–10.22)	0.002	5.65 (2.18–14.61)	< 0.001
Prior ipsilateral breast surgery, yes versus no	1.11 (0.68–1.82)	0.67			0.76 (0.34–1.69)	0.50		
Neoadjuvant chemotherapy, yes versus no	0.95 (0.51–1.77)	0.87			0.56 (0.18–1.68)	0.30		
Any axillary surgery, yes versus no	1.38 (0.91–2.08)	0.13			2.58 (1.39–4.80)	0.003	2.55 (1.32–4.93)	0.006
Periareolar incision, yes versus no	1.66 (1.01–2.73)	0.046			3.04 (1.60–5.75)	< 0.001		
Postoperative adjuvant radiation	Not assessed	–			3.30 (1.56–7.00)	0.002	3.22 (1.39–7.47)	0.007

tissue expander to implant-based reconstruction reported overall rates of surgical-site infection of 12%, skin necrosis 11%, nipple necrosis 5%, unplanned reoperation 9%, seroma requiring treatment 5%, and hematoma 1%.[27] Among single-institution retrospective studies clearly defining complications, rates of significant surgical-site infection have ranged from 2 to 9%,[15,26,28–30] seroma requiring treatment 1–5%,[29,31] and hematoma 1–3%.[20,26,28,29] More has been published specifically on mastectomy skin flap and nipple ischemia and necrosis. Reported rates of reversible ischemia and/or superficial epidermolysis of the nipple range from 6 to 13% [26,28,30,31] with significant nipple–areolar complex necrosis rates resulting in nipple loss occurring in 1–5% of cases.[15,20,23,25,26,28,32] In line with our observations, others also have shown that placement of incisions away from the areola is associated with fewer ischemic complications of the nipple–areolar complex.[1,24,33] Mastectomy skin flap ischemia rates of 4–20% and necrosis rates of 3–12% have been reported following NSM.[7,15,28,29,31]

As indications for NSM have become less stringent, more patients are undergoing NSM for ipsilateral cancer recurrence following prior breast-conserving surgery with radiation. It is well recognized that these patients have a higher risk of complications following mastectomy with immediate reconstruction with the tissue expander to implant-based approach, although there is little data specifically addressing NSM after prior radiation. One study evaluating 85 patients treated with prior whole-breast radiation and subsequent NSM found a substantial risk of infection (20%) and expander loss (15%) at the first stage of reconstruction.[34] The rate of implant loss was 5%. Another retrospective study of 69 NSMs in patients treated with prior radiation reported a substantial rate of early postoperative complications including infection, necrosis, and hematoma requiring reoperation of 18.8% as well as significant rates of nipple necrosis and nipple loss of 7.2% and 4.3%, respectively.[25]

As patients with more advanced disease undergo NSM, a greater proportion will be recommended for postmastectomy radiation (PMRT). Treatment with PMRT following expander/implant-based reconstruction substantially increases complication rates following definitive (second-stage) reconstruction. One study evaluated 133 NSMs treated with PMRT and reported a surgical-site infection rate of 31% and an implant loss rate of 15%.[34] The implant loss rate in this study was not higher than that reported for skin-sparing mastectomy of 20–30%,[35] although an earlier study of 99 patients from the same institution found higher reconstructive failure rates with PMRT after NSM than skin-sparing mastectomy (21% versus 13.5%).[36] Another study of 97 patients treated with PMRT reported lower rates of implant loss (8.2%) but a nipple loss rate of 4.1% and unplanned reoperation rate of 22%.[25] Various techniques such as the use of acellular dermal matrix and rapid expansion followed by deflation of tissue expanders while PMRT is administered continue to be explored to improve outcomes of this approach.[34,37]

In addition to evaluation of early postoperative complication rates, we addressed the success of reconstruction at 1 year. In the absence of prior or subsequent radiation discussed above, the long-term success of reconstruction following NSM, while variably defined and not consistently reported, has been ~ 95% across several studies.[25,38] Our results compare favorably with these reports despite the inclusion of higher-risk patients, finding that the vast majority of women were successfully reconstructed at 1 year from their index operation.

Limitations of this study include those inherent to a retrospective evaluation of a prospectively ascertained single tertiary care institution patient cohort treated by dedicated, fellowship-trained breast surgical oncologists and reconstructive surgeons. The study also had low power to assess the impact of some risk factors given their low prevalence. Further, while we do report on reconstructive success rates, we did not evaluate either cosmesis scores or cosmetic or other patient-reported outcomes. However, the advantages of the study include evaluation of a large and contemporary cohort of NSM patients operated on for a broad spectrum of indications.

CONCLUSIONS

We observed a decrease in 30-day complications of NSM requiring treatment, despite broadened indications among higher-risk patients over time. These data confirm a team learning curve with NSM and also demonstrate that the nipple-sparing approach is suitable for appropriately selected higher-risk patients for both risk reduction and cancer treatment.

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