Cancer and Clinical Oncology; Vol. 5, No. 1; 2016
ISSN 1927-4858 E-ISSN 1927-4866
Published by Canadian Center of Science and Education

Nipple-Sparing Mastectomy via Inframammary Fold: Reconstructive Red Flags

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Received: March 23, 2016 Accepted: April 22, 2016 Online Published: April 26, 2016

doi:10.5539/cco.v5n1p102 URL: http://dx.doi.org/10.5539/cco.v5n1p102

Abstract

Background: Nipple-sparing mastectomy (NSM) is a technically feasible and oncologically sound option for patients who meet eligibility criteria. Inframammary fold (IMF) incision results in a well-hidden scar and enhanced final aesthetic result. While oncologic eligibility criteria have been well established, reconstructive criteria are less defined. We report Moffitt Cancer Center's (MCC) outcomes with IMF incision for NSM and immediate reconstruction, and factors associated with increased complication rate.

Methods: IRB approved retrospective cohort study of patients who underwent NSM through an IMF approach with immediate reconstruction at MCC from 2006-2013 was conducted. Analysis included patient demographics, tumor characteristics, ancillary treatment, reconstructive method, and nipple and skin flap necrosis. A literature review was performed to compare outcomes with other types of incisions.

Results: 115 patients met inclusion criteria, representing 199 breasts. The average age was 48.1 (range 18-74). The two main complication categories evaluated were nipple necrosis (8%) and skin flap necrosis (10.6%). Older age demonstrated a significant relationship with skin flap necrosis (p=0.0155) and overall complications (p=0.0492). Complication rate was significantly higher in the cancer side vs. prophylactic side in patients who underwent bilateral mastectomies (p=0.0088). Factors with trends related to increased skin flap necrosis included increased mastectomy specimen weight (p=0.0704), smoking (p=0.0726), and significant comorbidities (p=0.0665).

Conclusion: Our institution's results substantiate that NSM through an IMF approach with immediate reconstruction is a viable option. Recognized risk factors such as age, laterality, breast weight, smoking history, and comorbidities associated with increased complications should be considered when determining patient selection for reconstruction.

Keywords: breast cancer; inframammary; mastectomy; nipple-sparing; reconstruction

1. Introduction

Nipple-sparing mastectomy (NSM) continues to gain popularity as a viable option for prophylactic and therapeutic surgical treatment of breast cancer in patients who meet inclusion criteria. Data from numerous series of NSM demonstrate that it is oncologically appropriate in patients with tumors that are at least 2 cm away from the base of the nipple, less than 3 cm in diameter, no clinical lymphadenopathy with negative sentinel node, no skin involvement, non- inflammatory breast cancer, no clinical nipple signs (retraction, bleeding, discharge, or pruritus), a unifocal tumor, and with a negative pathological section from intraoperative sampling of the nipple base (Spear, Hannan, Willey, & Cocilovo, 2009; Vlajcic, Zic, Stanec, Lambasa, Petrovecki, & Stanec, 2005; Laronga, Kemp, Johnston, Robb, & Singletary, 1999; Gerber, Krause, Dieterich, Kundt, & Reimer, 2009; Benediktsson & Perbeck, 2008; Stolier & Wang, 2008; Lagios, Gates, Westdahl, Richards, & Alpert, 1979; Gulben, Yildirim, & Berberoglu, 2009; Verma, Kumar, & Joshi, 1997; Smith, Payne, & Carney, 1976). With

careful patient selection and direct sampling/pathological evaluation of the sub-areolar tissue intraoperatively, NSM can be safely performed within oncological parameters.

Nipple-areola complex sparing mastectomy with IMF approach has been demonstrated to have lower nipple and skin necrosis rates compared to other types of incisions, with the additional advantage of a well-hidden scar. Our objective was to identify patient and breast specific variables associated with complications of skin flap and nipple necrosis in patients undergoing nipple-sparing mastectomy via an inframammary fold incision with immediate breast reconstruction. These findings aim to assist in establishing reconstructive criteria to further guide appropriate patient selection.

2. Patients and Methods

2.1 Data Collection

With approval by Moffitt Cancer Center (MCC) and the University of South Florida Institutional Review Board, we conducted a retrospective cohort study of patients who underwent a unilateral or bilateral nipple-sparing mastectomy through an inframammary incision with immediate breast reconstruction at MCC between 2006 and 2013. Standardized data abstraction forms created by the breast department were utilized to ensure thorough data collection for all patients. Follow-up ranged from one to seven years and included clinic visits in which there was evaluation by the attending plastic surgeon. Few patients were lost to follow-up prior to one year post-operatively, and they were excluded from the study. The primary author reviewed 121 charts, and data was crosschecked by the co-authors to minimize data extraction errors. Inclusion criteria for nipple sparing mastectomy through an inframammary incision was based on MCC guidelines (Figure 1). Study size was

Inclusion Criteria: Patients must meet **all** of the following criteria. **Yes** must be marked for all Inclusion. **N/A** can only be marked for those not blacked out.	**Yes**	**No**	**N/A**
All patients who will be surgically treated for breast cancer at Moffitt Cancer Center (MCC) with a mastectomy and immediate reconstruction will be eligible for this study if all of the following criteria are met:			
1. The cancer is unifocal and the histology is ductal carcinoma is situ (DCIS), invasive ductal, invasive lobular, or a sarcoma. **Date of Note:**_____	[ ]	[ ]	■
2. The area of cancer (histologies aforementioned), is 5cm. or smaller based on pre-operative breast imaging. **Date of Note:**_____	[ ]	[ ]	■
3. The tumor margin is greater than 2cm from the areola edge based radially and 2cm from the posterior margin of the nipple-areola base based on pre-operative breast imaging. **Date of Note:** _____	[ ]	[ ]	■
4. Clinically the patient is lymph node-negative and having a sentinel lymph node biopsy at the time of the mastectomy on the cancer side (not required on a prophylactic mastectomy). **Date of Note:**_____	[ ]	[ ]	■
Note: All patients who will have a prophylactic mastectomy (unilateral or bilateral) for risk reduction will be eligible for a nipple-sparing mastectomy of the breast without cancer.			

Exclusion Criteria: Any of the following is a criterion for **exclusion** from the study: **No** must be marked for all exclusion. **N/A** only for those not blacked out.	**Yes**	**No**	**N/A**
1. Patients under the age of 18 and patients over the age of 85 at the time of surgery. **Date of Birth:**_____	[ ]	[ ]	■
2. Extensive Ductal Carcinoma In Situ greater than 5cm in total area. **Date of Note:**_____	[ ]	[ ]	■
3. Previous history of irradiation to the breast area (i.e. Mantle radiation for lymphoma) **Date of Note:**_____	[ ]	[ ]	■
4. Previous history of nipple-areola surgery (duct excision, circumareolar incisions) within last 3 years. **Date of Note:**_____	[ ]	[ ]	■
5. The invasive cancer is greater than 5cm in size, is multicentric, is within 2cm from the areola margin or is within 2cm from the posterior aspect of the nipple-areola base. **Date of Note:**_____	[ ]	[ ]	■
6. Clinically suspicious axillary lymph nodes on palpation or by fine needle aspiration. **Date of Note:**_____	[ ]	[ ]	■
7. History of smoking within 6 weeks of intended surgery. **Date of Note:**_____	[ ]	[ ]	■
8. Obesity (defined as BMI of greater than 35**). Date of Note:**_____	[ ]	[ ]	■
9. Not a candidate for immediate breast reconstruction. **Date of Note:**_____	[ ]	[ ]	■
10. Not a candidate for nipple sparing mastectomy due to breast size is >700 grams or significant contour abnormalities of the nipple-areola complex itself. **Date of Note:**_____	[ ]	[ ]	■

Figure 1. Moffitt Cancer Center Nipple-Sparing Mastectomy Eligibility Checklist

established by identifying patients who underwent the procedure of interest within the designated period, met oncologic eligibility criteria, and had sufficient follow-up. These explicit criteria determined patient selection for inclusion in the retrospective chart review.

The following data was extracted for each patient: age, race, BMI, smoking history, comorbidities, history of chemotherapy or radiation therapy, previous lumpectomy, unilateral or bilateral cancer, unilateral or bilateral mastectomy, excised breast weight, type of reconstruction, tissue expander fill volume, implant volume, skin flap necrosis, nipple necrosis, and any complication. All predictors were measured at the time of surgery, and complications were assessed as occurring within the sixty-day postoperative period. Primary outcome variable of interest was overall complication, particularly skin flap and/or nipple necrosis.

Potential confounding factors include previous lumpectomy and mastectomy technique, for example, scissor versus electrocautery dissection. Factors considered potential effect modifiers were age at time of surgery, comorbidities, social history, breast volume, and size of expander/implant, all of which were included in the statistical analysis. Sources of data for these variables were identified in the patient's chart; patient age, breast volume, and size of expander/implant were continuous quantitative data that did not need to be grouped. Qualitative variables including comorbidities, related treatments, and smoking and/or alcohol history were designated with a binary variable. We examined quantitative variables that could contribute to any complication, particularly those of skin flap and/or nipple necrosis, and grouped them according to patient or breast specific variables.

Potential sources of bias include discrepancy between observer assessments of skin flap or nipple necrosis. To minimize bias, patients who had reconstruction from non-primary MCC plastic surgeons were excluded, generally due to insufficient follow-up or non-standardized objective post-operative evaluation. The vast majority of patients had reconstruction performed by the senior author, and therefore pre and post-operative assessment of all patients was consistent. Furthermore, clinical documentation by all relevant providers (ie: attending surgeon, resident, nursing notes) was reviewed, and any mention of nipple or skin flap compromise from epidermolysis to full thickness loss was included and noted as a complication.

Standard breast markings made preoperatively included: midline, meridian, IMF, tangent from the inferior point of the IMF across the midline, dashed lines to denote 1 cm lateral from midline bilaterally, and dashed lines to mark the upper border of the breast mound. An 8-11 centimeter incision was made along the inframammary fold curving up laterally following the breast crease. Mastectomy was performed by the breast surgeon with either scissor or electrocautery dissection based on his/her preference, without use of tumescent infiltration. Fluorescent angiography or woods lamp assessment of the mastectomy skin flaps was not performed, as these modalities are not routinely employed at our facility for this procedure. Intraoperative nipple base samples were sent to pathology for frozen section evaluation, and axillary sentinel lymph node biopsy was performed in all patients with known breast cancer. Once the nipple base margins and sentinel node biopsies were confirmed negative for carcinoma, reconstruction was begun. Reconstruction was performed by one of two plastic surgeons, with the majority of cases performed by the senior author.

The main type of reconstruction was tissue expander reconstruction, with a small subset undergoing latissimus dorsi flap and tissue expander reconstruction. We favor total submuscular coverage in skin-sparing mastectomy followed by expander placement. The pectoralis major muscle was dissected laterally, creating a submuscular pocket equivalent to pre-measured base width size. The serratus anterior muscle or fascia was lifted off the anterior chest wall, the expander was inserted, and the muscles were reapproximated using 3.0 Vicryl interrupted suture. Expanders were then inflated with a variable amount of saline based on plastic surgeon discretion. Standard surgical technique included insertion of one 15 french Jackson-Pratt drain placed subcutaneously in each breast pocket, and secured with a 3.0 Nylon suture. The skin was closed in a layered fashion using 3.0 monofilament deep dermal sutures followed by a 4.0 monofilament running subcuticular closure. Post-operative course generally consisted of one to two days of routine inpatient hospital stay. Clinic follow-up was scheduled within five days following discharge, and removal of drains occurred when output of each drain was less than thirty milliliters for two consecutive twenty-four hour periods.

2.2 Statistical Analysis

Statistical analysis performed by the Biostatistics department at Moffitt Cancer Center included descriptive statistics for both patient and breast level variables. When comparing variables to overall complications or presence of skin flap or nipple necrosis, p-values were calculated using generalized linear model adjusting for correlation within patient ID, and are from separate single variable models. Six patients had missing data or inadequate follow-up; these individuals were representative of the original study sample, and due to the small

number, they were excluded from the study. All p-values are two-sided, and considered statistically significant at the 0.05 level. All statistical analyses were performed using SAS (version 9.3; SAS Institute; Cary, NC).

3. Results

Of the 441 patients in the Moffitt Cancer Center breast surgery research database from 2006 to 2013, 121 patients had nipple-sparing mastectomy with immediate reconstruction. Among them, 115 patients were identified who met full inclusion criteria, representing 199 breasts. The mean (±SD) age was 48.0 ± 10.3 years (range 18-74). One hundred patients underwent immediate breast reconstruction with tissue expander reconstruction, and nine patients underwent latissimus dorsi flap (LD) with tissue expander reconstruction. LD was performed in patients who had unilateral NSM to achieve optimal symmetry with the contralateral unaffected breast, patients who desired autologous reconstruction but were not candidates for, or opted against, use of abdominal tissue, and in patients with a history of radiation therapy. Routine use of single stage implants was not employed at our facility during this study. Average total tissue expander fill volume was 228.9 mL (range 50-700 ml), and average final implant volume was 534.04 cc.

Acellular dermal matrix was not utilized in these patients due to adequate mastectomy tissue flap thickness and effective total muscular coverage of the expander. Radiation therapy was indicated as 'any radiation' or 'no radiation'; 23 patients received radiation, 92 patients did not. 14 of the 23 patients received adjuvant radiation therapy following mastectomy and 9 had a remote history of radiation following previous lumpectomy. The majority of patients had unilateral breast cancer and underwent bilateral NSM (Table 1). Any patient with positive nipple margins was ineligible for NSM and therefore excluded from the sample group. The potential confounding factor of previous lumpectomy was evaluated and was determined to have no statistical relationship with skin flap or nipple necrosis ($p = 0.2011$ and 0.7580, respectively). The two main complications evaluated were skin flap and/or nipple necrosis. Our results demonstrated a 10.6% rate of skin flap necrosis, and 8% rate of nipple necrosis (Table 2). All objective flap or nipple-related complications ranging from epidermolysis or partial thickness loss treated with local wound care, to full-thickness loss necessitating reconstruction, were included in the calculation of necrosis.

Table 1. Patient specific variables

Variable	N; Mean (STD); Median [Range]
Age	n=115; 48.09(10.24); 48 [18,74]
BMI	n=113; 22.77(2.47); 22.8 [17,29.8]

Patient demographics	Variable	Percent
Race	White	88.70
	Non-White	11.30
Ever Smoked	No	74.78
	Yes	25.22
Any Co-morbidities	No	50.43
	Yes	49.57
Chemotherapy	No	64.35
	Yes	35.65
Radiation	No	80.0
	Yes	20.0
Bilateral/Unilateral Cancer	Bilateral	8.70
	None (prophylactic)	14.78
	Unilateral	76.52
Bilateral/Unilateral NSM	Bilateral	76.52
	Unilateral	23.47
Latissimus Dorsi Flap	No	92.17
	Yes	7.83

Table 2. Breast specific variables

Variable	N; Mean(STD); Median [Range]
Breast weight	n=185; 373.99(167.75); 337.5 [41,880]

Breast specific	Variable	Percent
Breast Side	Left	51.26
	Right	48.74
Skin Flap Necrosis	No	89.44
	Yes	10.55
Nipple Necrosis	Yes	8.04
	No	91.96
Cancer Side	Cancer Side	50.40
	Non-Cancer Side	49.60

Table 3. Skin flap necrosis in relation to patient demographics

Variable	N; Mean(STD); Median [Range]		P Value
	No Skin Flap Necrosis	Skin Flap Necrosis	
Age	n=178; 46.77(9.99); 47 [18,74]	n=21; 53.86(8.58); 54 [42,71]	0.0155
BMI	n=176; 22.78(2.56); 22.8 [17,29.8]	n=21; 23.18(1.92); 22.7 [20.6,27.5]	0.3638
Breast Weight	n=164; 366.4(169.2); 330.5 [41,880]	n=21; 433.3(146.23); 437 [225.7,765.5]	0.0704
TE Fill Amount	n=142; 227.53(125.39); 200 [50,680]	n=17; 240.59(144.33); 200 [100,700]	0.5764

Variable		N (%)		P Value
		No Skin Flap Necrosis	Skin Flap Necrosis	
Ever Smoked	No	137 (93.2%)	10 (6.8%)	0.0726
	Yes	41 (78.8%)	11 (21.2%)	
Any Co-morbidities	No	96 (94.1%)	6 (5.9%)	0.0665
	Yes	82 (84.5%)	15 (15.5%)	
Bilateral/Unilateral Cancer	Bilateral	17 (94.4%)	1 (5.6%)	0.5440
	None (prophylactic)	26 (86.7%)	4 (13.3%)	
	Unilateral	135 (89.4%)	16 (10.6%)	
Previous Lumpectomy	No	127 (87.6%)	18 (12.4%)	0.2011
	Yes	51 (94.4%)	3 (5.6%)	
Chemotherapy	No	112 (87.5%)	16 (12.5%)	0.3823
	Yes	66 (93%)	5 (7%)	
Radiation	No	140 (88.6%)	18 (11.4%)	0.5288
	Yes	38 (92.7%)	3 (7.3%)	
Bilateral/Unilateral NSM	Bilateral	156 (90.7%)	16 (9.3%)	0.2339
	Unilateral	21 (80.8%)	5 (19.2%)	
TE Placed	No	17 (89.5%)	2 (10.5%)	0.7907
	Yes	161 (89.4%)	19 (10.6%)	
Cancer Side	Cancer Side	57 (90.5%)	6 (9.5%)	0.3204
	Non-Cancer Side	57 (91.9%)	5 (8.1%)	

Table 4. Nipple necrosis in relation to patient demographics

Variable	N; Mean(STD); Median [Range]		P Value
	No Nipple Survival	Nipple Survival	
Age	n=17; 45.41(7.3); 45 [33,60]	n=182; 47.71(10.28); 47 [18,74]	0.4446
BMI	n=16; 23.92(2.73); 24.27 [19.8,26.7]	n=181; 22.72(2.46); 22.7 [17,29.8]	0.1718
Breast WT	n=15; 393.2(123.56); 374.1 [209,589.9]	n=170; 372.3(171.28); 333.7 [41,880]	0.5413
TE Fill Amount	n=13; 230.77(138.71); 250 [80,530]	n=146; 228.76(126.54); 200 [50,700]	0.9650

Variable		N (%)		P Value
		No Nipple Survival	Nipple Survival	
Any Co-morbidities	No	8 (7.8%)	94 (92.2%)	0.6541
	Yes	9 (9.3%)	88 (90.7%)	
Bilateral/Unilateral Cancer	Bilateral	4 (22.2%)	14 (77.8%)	0.3961
	None (prophylactic)	4 (13.3%)	26 (86.7%)	
	Unilateral	9 (6%)	142 (94%)	
Previous Lumpectomy	No	12 (8.3%)	133 (91.7%)	0.7580
	Yes	5 (9.3%)	49 (90.7%)	
Chemotherapy	No	12 (9.4%)	116 (90.6%)	0.5129
	Yes	5 (7%)	66 (93%)	
Radiation	No	11 (7%)	147 (93%)	0.2321
	Yes	6 (14.6%)	35 (85.4%)	
Bilateral/Unilateral NSM	Bilateral	15 (8.7%)	157 (91.3%)	0.8672
	Unilateral	2 (7.7%)	24 (92.3%)	
TE Placed	No	1 (5.3%)	18 (94.7%)	0.7352
	Yes	16 (8.9%)	164 (91.1%)	
Latissimus Dorsi Flap	No	15 (8.2%)	169 (91.8%)	0.4796
	Yes	2 (13.3%)	13 (86.7%)	
Cancer Side	Cancer Side	4 (6.3%)	59 (93.7%)	0.3243
	Non-Cancer Side	2 (3.2%)	60 (96.8%)	

Older age was found to have a significantly higher prevalence of skin flap necrosis; mean age of patients with necrosis was 53.9 years (range 42-71) compared to 46.8 years (range 18-74) of those that did not experience this complication ($p = 0.0155$). A trend was noted between greater excised breast weight and frequency of skin flap necrosis ($p = 0.0704$). Among patients with skin flap necrosis, a higher percentage had a history of smoking (21.2% vs. 6.8%; $p = 0.0726$) and other comorbidities such as hypertension and diabetes (15.5% vs. 5.9%; $p = 0.0665$) (Table 3). With regards to nipple necrosis, there were no identifiable trends (Table 4). Interestingly, our data demonstrated that patients who received adjuvant chemotherapy had a lower proportion of complications than those who did not ($p = 0.0503$). In patients who underwent bilateral mastectomies for unilateral cancer, there was a 1.5 times higher proportion of complications on the breast cancer side compared to the prophylactic side ($p = 0.0088$) (Table 5).

Pre-operative and post-operative photographs of three representative patients who each underwent bilateral nipple-sparing mastectomy via an IMF incision are illustrated in Figures 2-3.

Table 5. Complication rates in relation to patient demographics

Variable	N; Mean(STD); Median [Range]		P Value
	No Complications	Any Complication	
Age	n=109; 45.9(10.13); 45 [18,74]	n=90; 49.48(9.69); 49 [18,71]	0.0492
BMI	n=108; 22.83(2.54); 22.85 [17,29.8]	n=89; 22.8(2.46); 22.7 [17.8,28.1]	0.8639

Variable		N (%)			P Value
		Number of patients	No Complications	Any Complication	
Ever Smoked	No	147 (73.9%)	84 (57.1%)	63 (42.9%)	0.2999
	Yes	52 (26.1%)	25 (48.1%)	27 (51.9%)	
Any Co-morbidities	No	102 (51.3%)	58 (56.9%)	44 (43.1%)	0.6988
	Yes	97 (48.7%)	51 (52.6%)	46 (47.4%)	
Previous Lumpectomy	No	145 (72.9%)	78 (53.8%)	67 (46.2%)	0.7646
	Yes	54 (27.1%)	31 (57.4%)	23 (42.6%)	
Chemotherapy	No	128 (64.3%)	62 (48.4%)	66 (51.6%)	0.0503
	Yes	71 (35.7%)	47 (66.2%)	24 (33.8%)	
Radiation	No	158 (79.4%)	90 (57%)	68 (43%)	0.2653
	Yes	41 (20.6%)	19 (46.3%)	22 (53.7%)	
Bilateral/Unilateral NSM	Bilateral	172 (86.9%)	91 (52.9%)	81 (47.1%)	0.2527
	Unilateral	26 (13.1%)	17 (65.4%)	9 (34.6%)	
Cancer Side	Cancer Side	63 (50.4%)	32 (50.8%)	31 (49.2%)	0.0088
	Non-Cancer Side	62 (49.6%)	41 (66.1%)	21 (33.9%)	

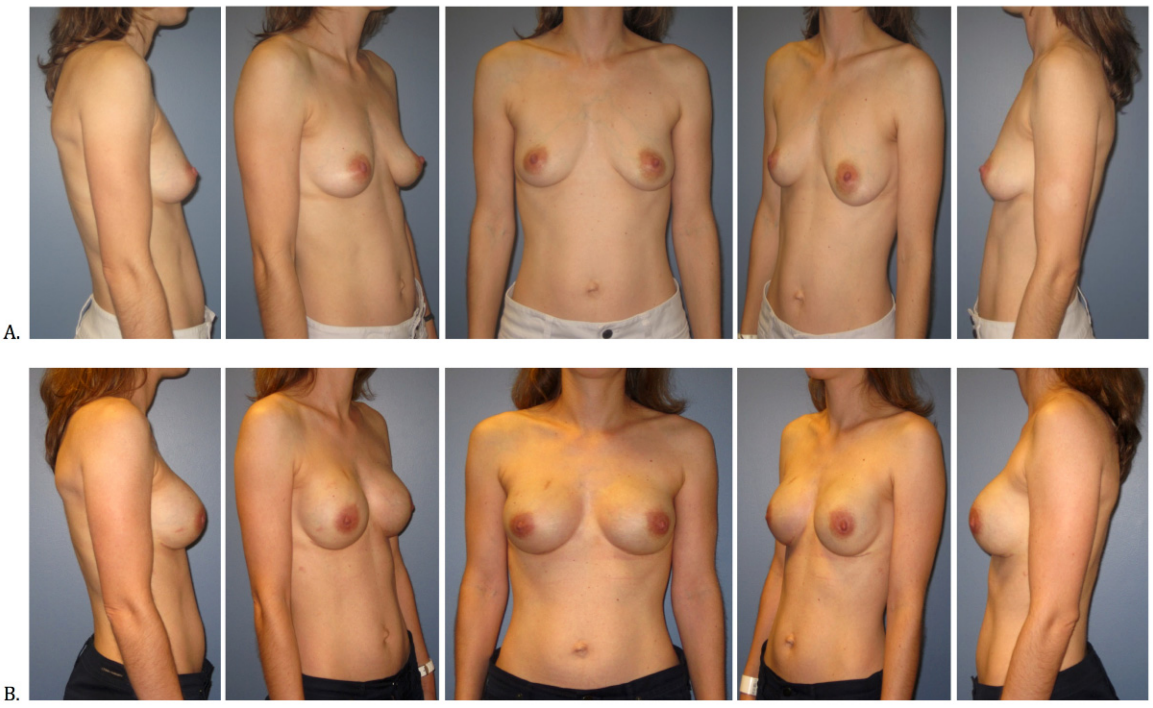

Figure 2. 37 year old female with strong family history of breast cancer. A. pre-operative; B. post-operative after prophylactic bilateral NSM via IMF incision with tissue expander and silicone breast implant reconstruction

Figure 3. 57 year old female with left DCIS. A. pre-operative; B. post-operative after bilateral NSM via IMF incision with tissue expander and silicone breast implant reconstruction

4. Discussion

Long-term follow-up in breast cancer survivorship has demonstrated that NSM is as oncologically sound as other types of mastectomy. Secondary to oncologic criteria for NSM is reconstructive criteria, with a focus on factors associated with skin flap and nipple necrosis. While there are less objective measures, basic guidelines that have been proposed include small to moderate breast size, minimal to moderate ptosis, and satisfactory skin quality (Sacchini et al., 2006; Caruso et al., 2006). Other suggested considerations for reconstructive criteria include appropriate incision placement, employing caution in patients with large breasts with previous scars, patients with prior breast/chest radiation therapy, and in individuals who are smokers or diabetics (Salgarello, Visconti, & Barone-Adesi, 2010). Our results demonstrate that nipple-sparing mastectomy via IMF incision is an efficient procedure with a prevalence of 10.6% skin flap necrosis and 8% nipple necrosis. This approach has the lowest complication in patients who are younger, non-smokers, smaller breast sized, generally healthy with no or minimal medical comorbidities, and on the prophylactic mastectomy breast.

Two of the main complications of immediate reconstruction following NSM are skin flap and nipple necrosis. While extent of resection and type of breast reconstruction contribute to the risk of complication, incision placement has a profound effect, particularly with regard to nipple necrosis. Our results of 10.6% skin flap necrosis and 8% NAC necrosis are lower compared to non-IMF incisions reported in other studies, and our results are consistent with those reported in the literature for IMF incisions. Other surgical approaches to NSM that have been described include periareolar, inframammary, vertical, transareolar, radial, and an incision placed at the site of a previous scar.

A systematic review of English articles using the PubMed, MEDLINE, Ovid, Cochrane databases, and reference lists of relevant articles was performed. We used the following key terms to search all databases: nipple-sparing mastectomy, inframammary fold, immediate reconstruction, skin flap necrosis, nipple necrosis, and reconstructive criteria. The literature reflects a wide range of nipple-areolar complex necrosis rates between 0-48% (Salgarello et al., 2010; Rusby, Smith, & Gui, 2010; Wijayanayagam, Kumar, Foster, & Esserman, 2008; Petit et al., 2006; Bistoni, Rulli, Izzo, Noya, Alfano, & Barberini, 2006; de Alcantara Filho, Capko, Barry, Morrow, Pusic, & Sacchini, 2011; Harness, Vetter, & Salibian, 2011; Jensen, Orringer, & Giuliano, 2011; Margulies, Hochberg, Kepple, Henry-Tillman, Westbrook, & Klimberg, 2005; Sacchini et al., 2006; Spear et al., 2011; Djohan et al., 2010; Crowe et al., 2004; Colwell et al., 2014; Salibian, Harness, & Mowlds, 2013; Endara, Chen, Verma, Nahabedian, & Spear, 2013). In their recent review of 113 cases of NSM with immediate breast

reconstruction, Gould et al. (2013) found that their overall incidence of any (partial or total) nipple necrosis was 20% via a non-IMF approach. In a review of 64 NSM via various approaches, Wijayanayagam et al. noted a total NAC necrosis rate of 20%, partial NAC necrosis 84%, and total skin-sparing skin flap necrosis of 17%. NSM via IMF incision had 0% necrosis, whereas NAC-crossing incisions had 81.8% partial necrosis, leading the authors to conclude that incisions spanning >1/3 of the NAC circumference likely compromised blood supply, resulting in nipple-areola skin necrosis (Wijayanayagam et al., 2008). Direct comparison of two cohorts of total skin-sparing mastectomies that differed in extent of NAC involved in the incision illustrated that periareolar incisions involving more than 30% of the circumference of the areola are at an increased risk of NAC necrosis, and along with other variables, adjusting the incision contributed to a significant reduction in nipple necrosis rates from 20% to 5% (Garwood et al., 2009). Furthermore, in a comprehensive literature search that included 6615 NSM, incision types were divided into five categories: radial, periareolar/circumareolar, inframammary, mastopexy, and transareolar, and found to have nipple necrosis rates of 8.83, 17.81, 9.09, 4.76, and 81.82%, respectively (Endara et al., 2013). Several other studies similarly corroborate these substantial differences in rates of NAC necrosis based on incision placement, with the IMF approach having the lowest rate of complication (Salgarello et al., 2010; Colwell et al., 2014; Endara et al., 2013; Chen et al., 2009). Placement of the incision in the IMF has been demonstrated to both preserve arterial supply to the NAC and to bolster the new IMF (Colwell et al., 2014; Chen et al., 2009; Margulies et al., 2005).

Regarding specific reconstructive criteria, our results demonstrate that older age had a significant relationship with skin flap necrosis (p=0.0155) and overall complications (p=0.0492), consistent with the findings of other authors (Komorowski et al., 2005; Dent, Small, Swistel, & Talmor, 2014; Davies, Allan, Roblin, Ross, & Farhadi, 2011). This is likely due to dermal thinning and the effects of age-related concomitant medical comorbidities on wound healing. In our study, prevalence of complication was significantly higher in the breast cancer side compared to the prophylactic side in patients who underwent bilateral mastectomies for unilateral cancer (p=0.0088). A possible explanation for this may be inadvertent creation of thinner mastectomy flaps on the cancer side by the breast surgeon, or previous insult to the tissue on the cancer side from prior biopsy, lumpectomy, radiation, or tumor burden. Interestingly, our data demonstrated a trend of lower percentage of complication in those patients who received adjuvant chemotherapy compared to those who did not receive chemotherapy (p = 0.0503). While chemotherapy has largely been shown to delay wound healing, Peled, et al reviewed 163 patients who underwent mastectomy and immediate breast reconstruction comparing postoperative outcomes between women who received neoadjuvant chemotherapy, adjuvant chemotherapy, or no chemotherapy. Their results demonstrated no differences between groups in terms of planned return to the operating room, expander loss, and donor-site complications, and they concluded that the timing of chemotherapy relative to mastectomy did not significantly affect surgical outcomes (Pelod et al., 2010).

Factors that exhibited trends related to increased skin flap necrosis in our study included increased excised specimen weight (p=0.0704), smoking (p=0.0726), and medical comorbidities including hypertension and diabetes (p=0.0665), which supports existing literature (Djohan et al., 2010; Komorowski et al., 2006; Munhoz et al., 2013). The adverse effect of increased body mass index on breast reconstruction has been previously discussed, likely due to excessive stress placed on the subdermal plexus as well as comorbidities associated with obesity (Colwell et al., 2014; Alderman, Wilkins, Kim, & Lowery, 2002; Bailey et al., 1989; Mosahebi, Ramakrishnan, Gittos, & Collier, 2007). A possible explanation proposed for the relationship between resected tissue weight and complication is the notion that perfusion is decreased in larger skin flaps resulting from larger breasts. Included in their study involving 500 NSM procedures, Colwell et al. noted that smoking and periareolar incisions were positive predictors for total complications, and preoperative radiation treatment contributed to an increased rate of nipple necrosis (Colwell et al., 2014). In Dent et al's results of NSM through IMF with single or two-staged implant-based reconstruction, 20.4% of patients had partial thickness or full thickness NAC ischemia. The risk factors for NAC ischemia identified in their study included advanced age, increased BMI, greater breast volume, and history of diabetes mellitus. In these patients, conservative treatment failed if they also had a history of smoking, if they had undergone single-stage reconstruction, or if ADM had been utilized (Dent et al., 2014). In an evaluation of NSM via IMF in patients with previous lumpectomy, Huston et al. (2015) demonstrated an overall rate of 20.4% NAC ischemia. Conversely, they found no significant correlation between the incidence of NAC ischemia and various demographic and clinical factors including age, BMI, resection volume, prior radiation, ADM use, diabetes, or smoking history.

Of the 23 patients in our study that had radiation therapy, 14 had adjuvant therapy following mastectomy and 9 had a remote history of radiation treatment following previous lumpectomy. While the deleterious effects of radiation on tissue are well established, none of the above patients had a notably higher proportion of

complication.

Aesthetic results of nipple-sparing mastectomy cannot be underscored. NAC reconstruction can result in asymmetry with the contralateral NAC, decreased nipple projection, nipple loss, and unsatisfactory results involving color (depigmentation), size, position, and diminished or absent sensation. Research has demonstrated that patients who undergo NAC preservation report enhanced body image, psychological adjustment, and overall satisfaction compared to women who underwent mastectomy without nipple preservation (Chen et al., 2009; Billar, Dueck, Gray, Wasif, & Pockaj, 2011; Wellisch, Schain, Noone, & Little, 1987; Goh, Martin, Pandya, & Cutress, 2011). In Djohan et al.'s eight year outcome study surveying patients who underwent NSM with immediate reconstruction, a majority of patients rated appearance, symmetry, color, position, and texture as good or excellent, and 73.1% of responders stated they would definitely undergo NSM again (Djohan et al., 2010). Moreover, Didier et al's patient-reported outcome measures evaluating women with NAC preservation versus those who underwent NAC reconstruction after mastectomy, demonstrated statistically significant differences in favor of NAC preservation with regard to body image, nipple appearance, and nipple sensitivity. They similarly concluded that nipple-sparing mastectomy had a positive impact on overall patient satisfaction, body image, and psychological adjustment (Didier et al., 2009). Comparable findings have been demonstrated in patients undergoing TRAM reconstruction following NSM, where cosmetic outcomes were determined to be fair to excellent in the majority of patients. Evaluated against a baseline population, patients scored higher on average in physical functioning, vitality, emotional well-being, and general health categories (Dao & Verheyden, 2005). Interestingly, in their experience Peled et al. found that patients with greater preoperative breast size and/or more significant ptosis reported decreased nipple satisfaction as measured by the BREAST-Q (Peled et al., 2014).

Limitations to our study include retrospective analysis and possible confounding variables associated with mastectomy such as method of flap dissection (electrocautery versus sharp dissection). While the reconstructive technique was consistent among all cases, three different breast surgeons performed the mastectomies, and the nuances of their individual surgical technique may affect flap outcome. Future study includes direct comparison to other types of incisions within our institution, use of ADMs, single-stage implant reconstruction, follow-up of our findings regarding differing results between the cancer and prophylactic breasts, and controlling for variables in breast surgeon technique. Our results are applicable to other patients who undergo nipple-sparing mastectomy via an inframammary incision and immediate reconstruction. As a major national cancer center, our database encompasses patients with a broad range of ages, ethnicities, comorbid conditions, and disease severity. It may be less applicable to institutions that routinely employ fluorescent angiography or woods lamp assessment of the mastectomy skin flaps, as they can selectively determine which patients to perform immediate reconstruction.

5. Conclusion

Inframammary fold incision for nipple-sparing mastectomy has been demonstrated to be oncologically sound, efficacious, and results in superior outcomes with regard to camouflaged incision and decreased complications of nipple-areolar complex or skin flap necrosis compared to other approaches in the literature. Our result of 10.6% skin flap necrosis and 8% nipple necrosis is comparable to other studies utilizing an IMF approach, and lower than those involving other incisions. Prevalence of complications was found to be significantly higher in the breast cancer side vs. prophylactic mastectomy side in patients with bilateral mastectomies, and in patients with increasing age. Factors with trends related to increased skin flap necrosis included increased excised specimen weight, smoking, or significant comorbidities. Awareness of these factors will help further delineate reconstructive criteria for appropriate patient selection.

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