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1 **Nipple Sparing Mastectomy: A Review of Outcomes at a Single Institution**

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20 **Running Title:** A Review of Nipple Sparing Mastectomy

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24 **Key Words:** Nipple Sparing Mastectomy; Breast Surgery; Breast Cancer; Recurrence;
25 Malignancy

26 **Abstract**

27 **Introduction**

28 Nipple sparing mastectomy (NSM) offers patients who are not candidates for breast conserving
29 treatment an aesthetically pleasing alternative to traditional mastectomy. Some studies have
30 demonstrated its oncologic safety while others have demonstrated residual occult tumor cells at
31 the nipple areolar complex (NAC). These data prompt further review of oncologic outcomes
32 after NSM.

33 **Methods**

34 A single institution retrospective chart review of all NSMs performed by 4 breast surgeons at
35 Thomas Jefferson University Hospital over a span of 2012-2019. In this cohort we review the
36 reconstruction performed, axillary lymph node status, surgical margins, final pathology, loss of
37 the NAC, recurrence rates, and follow-up.

38 **Results**

39 In our cohort we reviewed 170 NSMs performed on 105 patients. All patients were female and
40 the average age was 46.9 years. Prophylactic procedures were performed on 43% of patients with
41 17.1% of patients being BRCA positive. Of those undergoing NSM for cancer (n=94) the
42 associated pathology was 28.8% DCIS, 32.9% IDC, and 3.5% ILC (This accounts for some
43 patients with multiple diagnoses on final pathology). Sentinel lymph node biopsy (SLNB) was
44 performed in 52.9% of cases with 10.6% of cases being positive for axillary disease. Margins
45 were positive in 10.6% (n=10) of cases performed for cancer with 8.5% (n=8) of cases having
46 positive margin at the NAC and the remainder being at the deep margin. Based on margin
47 positivity 2.4% (n=4) of patients underwent redo surgery with 1 patient requiring re-resection at

48 the NAC margin and 3 patients having total NAC resection. Total loss of NAC occurred in 5.9%
49 (n=10) of cases due to positive margins (n=3) and necrosis (n=7). Recurrence occurred in 7.2%
50 (n=7) of cases who underwent NSM for cancer. Locoregional recurrence in breast tissue, skin, or
51 axilla occurred in 4.1% (n=4) of cases with 0 recurrences at the NAC. Distant recurrence
52 occurred in 4.1% (n=4) of cases at both liver and bone. Average time to recurrence was 27.3
53 months. Of the 170 NSM performed 98% had immediate tissue expander placement with 60%
54 converting to permanent sub-pectoral implant reconstruction, 14% latissimus dorsi flap
55 reconstruction, 0.6% delayed deep inferior epigastric artery perforator free flap reconstruction,
56 and 5.2% undergoing delayed free transversus abdominus muscle flap reconstruction. Of all the
57 cases reviewed there was only 1 death. Our average follow-up was 26.7 months.

58 **Conclusions**

59 We demonstrate similar numbers in our analysis as other studies that have looked at oncologic
60 outcomes after NSM. Although we demonstrate evidence of occult disease at the NAC margin
61 when performing NSM there was no evidence of recurrence at the NAC demonstrating its
62 efficacy and safety. With proper patient selection this procedure can be safely offered as an
63 aesthetically appealing alternative to traditional mastectomy.

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65

66 **Introduction**

67 In oncoplastic surgery for breast cancer both oncologic and cosmetic outcomes are
68 important factors for procedure selection. When a patient with breast cancer undergoes surgery
69 the goal of the operation is to remove the cancer with a good oncologic result, as well as, provide
70 the patient with the desired cosmesis. Achieving quality aesthetic results after breast surgery
71 plays an important role in physical appearance and psychological body image which in turn can
72 affect patients' quality of life post-operatively.¹ The preservation of the nipple-areolar complex
73 (NAC) is a key factor in breast surgery aesthetics and therefore should be a consideration when
74 performing surgery for breast cancer.^{2,3}

75 In order to preserve the natural appearance of the breast surgeons and patients often opt
76 for lumpectomy, if possible, as it is the least invasive option in breast cancer surgery.
77 Lumpectomy, however, is not always an option in cases such as large tumors or multicentric
78 disease. In these cases patients traditionally have undergone mastectomy. Mastectomy has good
79 oncologic outcomes but is a more extensive procedure and alters the natural breast appearance.
80 One procedure that has been developed in recent years to help preserve the integrity and
81 aesthetics of the breast after mastectomy is the nipple sparing mastectomy (NSM). This allows
82 the surgeon to preserve the NAC when performing a mastectomy which has been shown to have
83 better cosmetic outcomes to traditional and skin sparing mastectomy.^{4,5} These outcomes have
84 resulted in positive impacts on patient satisfaction, body image, psychological adjustment, and
85 sexual wellbeing.^{5,6}

86 Although NSM has been shown to be aesthetically appealing its oncologic safety and
87 associated complications are two factors that bring its utility into question. NSM does leave a
88 small amount of residual breast tissue in the retroareolar space that creates a theoretical higher

89 risk of recurrence. This has led to further investigation of NSM. The presence of occult disease at
90 the NAC margin after NSM has been cited as anywhere from 3-10%.^{7,8,9} The presence of occult
91 disease at the NAC can lead to locoregional recurrence after NSM; this has been noted in 2-4%
92 of patients.^{10,11, 12} This rate is comparable to modified radical mastectomy (MRM) and skin
93 sparing mastectomy (SSM).¹³ The overall survival and disease free survival has also been found
94 to be comparable to MRM and SSM in retrospective studies.^{10,13} Complication rates of NSM
95 have been noted to be 2-22% with the most common complication being nipple necrosis.^{8,12,14} If
96 a patient experiences nipple necrosis it can often lead to patient dissatisfaction, poor aesthetic
97 result, further operative procedures and loss of the NAC. If proper patient selection is employed,
98 however, NSM can have acceptable oncologic outcomes with minimal complications.^{8,11,12}
99 Expanding on the knowledge of NSM oncologic outcomes and complications can lead to better
100 patient selection and increased use of this procedure in breast cancer patients. In this study we
101 review the outcomes of patients who have undergone NSM in order to better understand its
102 implications and substantiate its utility as a safe oncologic procedure.

103 **Methods**

104 After obtaining Institutional Review Board authorization, we performed a retrospective
105 chart review on all patients who underwent NSM at Thomas Jefferson University Hospital
106 between the years of 2012 and 2019. All procedures were performed by 4 different breast
107 surgeons with immediate and delayed reconstructions performed by a plastic surgery group
108 comprised of 3 different plastic surgeons. All patients were evaluated by a breast surgeon prior to
109 their procedure and deemed candidates for NSM. In this cohort we review the reconstruction
110 performed, surgical margins, axillary lymph node status, final pathology, loss of the NAC,
111 recurrence rates, and follow-up.

112 **Results**

113 *Demographics*

114 In our cohort we reviewed 170 NSMs performed on 105 patients. All patients were
115 female with an average age of 46.9 years. Indications for NSM were prophylactic/benign
116 pathology (43% with 17.1% being prophylactic for BRCA positivity), DCIS (28.8%), IDC
117 (32.9%), and ILC (3.5%) (Table 1). These numbers account for patients who were found to have
118 multiple diagnoses on final pathology. Sentinel lymph node biopsy (SLNB) was performed in
119 52.9% of cases with 10.6% of cases being positive for axillary disease.

120 *Nipple Areolar Complex*

121 On final pathology, margins were positive in 5.8% (n=10) of cases with 4.7% (n=8) of
122 patients having positive margin at the NAC and 2.4% of patients (n=4) with positive deep
123 margins (2 patients had both positive NAC and deep margins). Of the patients with positive
124 margins, 6 patients were monitored clinically, 1 patient underwent re-excision at the NAC, 1
125 patient underwent re-excision at the NAC followed by complete NAC resection, and 2 patients
126 underwent complete NAC resection initially. All operations performed for positive margins were
127 for patients with positive NAC margins, no further surgery was performed on patients with
128 positive deep margins. These numbers are summarized in Table 2.

129 There was a loss of the NAC in 6.4% (n=11) of cases due to both necrosis and positive
130 margin. NAC loss due to necrosis occurred in 4.1% of cases (n=7) while NAC loss due to
131 positive margin occurred in 2.3% (n=4) of cases (One patient had positive margin and
132 subsequently had both NAC's removed for symmetry accounting for the difference in NAC
133 excisions for positive margin discussed above).

134 *Reconstruction*

135 Of the 170 cases performed the final reconstructions varied from permanent subpectoral
136 implants (60%, n=102), latissimus dorsi flaps with permanent implant (14.1%, n=24), deep
137 inferior epigastric artery perforator (DIEP) free flap reconstruction (0.59%, n=1), and free
138 transversus abdominus muscle (TRAM) flap reconstruction (5.3%, n=9). All reconstructions
139 were delayed with nearly all (98%) having tissue expanders placed at the time of surgery. These
140 numbers are summarized in table 4. Of note 34 cases were lost to follow-up or reconstructions
141 were performed outside of our institution.

142 *Recurrence and Survival*

143 Out of the 96 procedures performed for breast cancer (excluding prophylactic cases),
144 there were recurrences in 7.2% (n=7) of patients. Locoregional recurrence was defined as
145 recurrence in ipsilateral breast tissue, skin, or axilla and occurred in 4.1% (n=4) of cases. Of the
146 patients with locoregional recurrence zero had recurrence at the NAC. Distant recurrence
147 occurred in 4.1% (n=4) of cases at both liver (n=2) and bone (n=2). Of note one patient had both
148 locoregional and distant recurrence. The average time to diagnosis of recurrence was 27.3
149 months ranging from 7 months to 50 months. Of the patients with recurrence the average
150 distance of tumor from NAC was 6.5 cm and initial staging ranged from 0-IIb. Of all the cases
151 reviewed there was only 1 death. Our average follow-up time was 26.7 months.

152 **Discussion**

153 Our results are comparable to the rest of the published literature reviewing oncologic
154 outcomes of NSM. Occult disease present at the NAC was of particular interest because it may
155 be the driving factor for recurrence after NSM. We had positive NAC margins in 4.7% of

156 patients which is comparable to the current literature being anywhere from 3-10%.^{7,8,9} In our
157 study we found locoregional recurrence in 4.1% of cases which is also similar to the current
158 published literature suggesting it to be in the range of 2-4%.^{10,11,12} This is also comparable to the
159 published local recurrence rates of standard mastectomy patients.^{13,15,16} Interestingly, however, in
160 our study we did not have any local recurrences at the NAC. All of the locoregional recurrences
161 were in the skin overlying the breast (none of which were involving the NAC) or in the axilla.
162 This suggests that having occult breast disease in the NAC or retroareolar tissue may not be
163 responsible for recurrences. The pathology of those with recurrence ranged from stage 0 to IIb
164 suggesting that recurrence was also not associated with advanced disease. Other studies have
165 found similar phenomena suggesting that it perhaps has to do with more aggressive tumor
166 biology rather than the pathology at the time of procedure or the procedure itself.⁷

167 In our study we did not find that local recurrence was associated with any specific factor
168 including pathology, neo-adjuvant chemo, post-mastectomy radiation, or reconstruction
169 performed. Our numbers, however, may be too small to be able to detect a significant difference
170 amongst these factors. Some studies, however, have suggested that there should be patient
171 selection criteria for NSM. These selection criteria include age less than 45, tumor size less than
172 3-5 cm, peripherally located, greater than 2 cm from NAC, no multicentricity, and clinically
173 negative nodes.^{8,11,12,14} There are also suggestions in the literature to thoroughly look for disease
174 intra-operatively in the subareolar tissue.^{11,12} In this study all patients had no evidence of disease
175 at the NAC pre-operatively with clinically negative nodes. The NAC was also inspected
176 intraoperatively with most patients having a separate sample of tissue taking from the subareolar
177 tissue. In our patients with recurrence the average distance from the NAC was 6.5 cm with no
178 patient having tumor within 3 cm of the NAC. Of our 7 recurrences 3 of them did have

179 multicentric tumor pre-operatively with 2 of them leading to distant recurrence and 1 having
180 locoregional recurrence. These numbers were too small to find any statistically significant
181 association with recurrence. This review supports the selection criteria outlined above although
182 further study with higher power and longer follow-up is suggested to better define these criteria.
183 With a better understanding of patient selection NSM may be offered to more patients with better
184 outcomes.

185 Loss of the NAC is another major factor when considering NSM. In this study 6.4% of
186 cases had loss of the NAC with a majority being secondary to necrosis. This is similar to other
187 numbers in the literature.^{8,12,14} We did not find any particular association with loss of NAC to
188 pathology, reconstruction performed, neo-adjuvant chemo or post-mastectomy radiation. Further
189 investigation with higher power is suggested for better investigation of patient selection.
190 Necrosis of the NAC is typically from devitalization of the tissue and poor blood supply. In this
191 way it would be useful to look at factors that would compromise blood flow to the NAC
192 including smoking status, history of diabetes, history of peripheral vascular disease, BMI,
193 thickness of the NAC flap, and surgical approach. Further study investigating these factors may
194 provide for patient selection factors leading to better cosmetic outcomes.

195 Overall this review supports the continued use of the NSM as an oncologically safe and
196 cosmetically appealing approach to the treatment of surgical breast cancer. Currently, with
197 proper patient selection and surgeon experience, this procedure has provided oncologic outcomes
198 that are comparable to that of other surgical approaches to breast cancer. This has lead to better
199 cosmesis, improved patient satisfaction and quality of life post-operatively. With continued study
200 of NSM we can refine our selection criteria to improve on these outcomes and, perhaps, be able
201 to better identify the right patient population for this procedure.

202 **DISCLOSURE**

203 There are no conflicts of interest.

204

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246 **Tables and Figures**

247 **Table 1: Summary of Surgical Pathology after Nipple Sparing Mastectomy:** This table
 248 summarizes the final pathology of all patients who underwent nipple sparing mastectomy. There
 249 were a total of 170 patients, however, this table accounts for patients who had multiple diagnoses
 250 at final pathology.

	Benign			DCIS	IDC	ILC	Other
	Non-BRCA	BRCA	Total				
Patients	45	29	74	49	56	6	4
Percent	26.4	17.1	43.5	28.8	32.9	3.5	2.4

251

252 **Table 2: Summary of Margin Positivity and Reoperation after Nipple Sparing**
 253 **Mastectomy:** This table summarizes patients who had positive margins on final pathology after
 254 nipple sparing mastectomy and their management. Two patients had both anterior and deep
 255 margins accounting for 10 total patients. Of those who underwent re-operation for positive
 256 margin one patient had re-resection followed by excision accounting for the total of 4 patients.

	Positive Margin			Management for positive NAC margin			
	Deep	Anterior/NAC	Patient Total	Non-Operative	Re-Operation		
					Re-Resection	Excise	Patient Total
Patients	4	8	10	6	2	3	4
Percent	2.4	4.7	5.8	3.5	1.1	1.8	2.4

257

258 **Table 3: Summary of Reconstruction Performed after Nipple Sparing Mastectomy:** This
 259 table summarizes the reconstruction performed after nipple sparing mastectomy. Implant=
 260 permanent subpectoral implant, Lat= latissimus dorsi flaps with permanent implant, DIEP= deep
 261 inferior epigastric artery perforator free flap reconstruction, TRAM= free transversus abdominus
 262 muscle flap reconstruction.

	<u>Implant</u>	<u>Lat</u>	<u>DIEP</u>	<u>TRAM</u>	<u>Unknown</u>
Cases	102	24	1	9	34
Percentage	60	14.1	0.59	5.3	20

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